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Protocol for the scientific opinion on the Tolerable Upper Intake Level of dietary sugars

European Food Safety Authority (EFSA)

Abstract

In June 2016, EFSA received a mandate from the national food competent authorities of five European countries (Denmark, Finland, Iceland, Norway and Sweden) to provide a dietary reference value (DRV) for sugars, with particular attention to added sugars. A draft protocol was developed with the aim of defining as much as possible beforehand the strategy that will be applied for collecting data, appraising the relevant evidence, and analysing and integrating the evidence in order to draw conclusions that will form the basis for the Scientific Opinion on sugars. As EFSA wished to seek advice from stakeholders on this draft protocol, the NDA Panel endorsed it for public consultation on 12 December 2017. The consultation was open from 9 January to 4 March 2018. A technical meeting with stakeholders was held in Brussels on 13 February 2018, during the consultation period. After consultation with stakeholders and the mandate requestors, EFSA interprets this mandate as a request to provide scientific advice on an Tolerable Upper Intake Level (UL) for (total/added/free) sugars, i.e. the maximum level of total chronic daily intake of sugars (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. The assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose) taken through the oral route. The health outcomes of interest relate to the development of metabolic diseases and dental caries. The final version of the protocol was endorsed by the EFSA Panel on Dietetic Products, Nutrition and Allergies on 28 June 2018.

Keywords: sugars, tolerable upper intake level, adverse effects, metabolic diseases, dental caries, protocol

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1. Introduction and scope of the protocol

This document outlines the protocol for the Scientific Opinion on the Tolerable Upper Intake Level of dietary sugars of the EFSA Panel on Nutrition, Dietetic Products and Allergies (NDA Panel), supported by the ad-hoc Working Group (WG) on sugars. This draft protocol has been developed with the aim of defining as much as possible beforehand the strategy that will be applied for collecting data (i.e. which data to use for the assessment and how to identify and select them), appraising the relevant evidence, and analysing and integrating the evidence in order to draw conclusions that will form the basis for the Scientific Opinion.

The protocol has been developed following the principles and process illustrated in the EFSA PROMETHEUS project (PROmoting METHods for Evidence Use in Scientific assessments) (EFSA, 2015a).

A draft of this protocol was open for public consultation from 9 January to 4 March 2018. The public consultation included a technical meeting with stakeholders held in Brussels on 13 February 2018. The draft protocol has been amended in view of the comments received. All comments received have been addressed and published in a technical report (EFSA, 2018).

2. Background and rationale of the mandate

In June 2016, the national food competent authorities of five European countries (Denmark, Finland, Iceland, Norway and Sweden) sent a request to the European Food Safety Authority (EFSA) in order to provide a dietary reference value (DRV) for sugars, with particular attention to added sugars, on the basis of most recent scientific evidence. After discussing the mandate at its plenary meeting on 22–23 September 2016, the NDA Panel asked for some clarifications to the requestors, particularly regarding the type of DRV to be established, the exposure of interest, the target population and the health outcomes to be considered. In February 2017, the requestors clarified that they were interested in a science-based cut-off value for a daily exposure to added sugars from all sources (i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing) which is not associated with adverse health effects. The target population for the assessment was defined as the general healthy population, including children, adolescents, adults and the elderly. The requestors also clarified that the request relates to an update of the EFSA's Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre (EFSA NDA Panel, 2010a) in relation to the effects of added sugars on nutrient density, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type 2 diabetes and dental caries in adults and children.

In the EFSA's 2010 opinion, the term 'added sugars' referred to sucrose, fructose, glucose, starch hydrolysates (glucose syrup, high-fructose syrup) and other isolated sugar preparations used as such or added during food preparation and manufacturing.

With regard to the effects of added sugar intake, the NDA Panel reached the following conclusions on the outcomes assessed:

- Micronutrient density of the diet: observed negative associations between added sugars intake and micronutrient density of the diet are mainly related to patterns of intake of the foods from which added sugars in the diet are derived rather than to the intake of added sugars per se. The available data are not sufficient to set an upper limit for (added) sugars intake.
- Glucose and insulin response: there are limited, and mainly short-term, data on the effects of high intakes of sugars on glucose and insulin response. Most studies do not find any adverse effects at intakes of predominantly added sugars up to 20–25% of total energy (E%), provided that body weight is maintained.
- Serum lipids: although there is some evidence that high intakes (> 20 E%) of sugars may increase serum triglycerides and cholesterol concentrations, the available data are not sufficient to set an upper limit for (added) sugar intake.
- Body weight: the evidence relating high intake of sugars (mainly as added sugars), compared to high intakes of starch, to weight gain is inconsistent for solid foods. However, there is some evidence that high intakes of sugars in the form of sugar-sweetened beverages (SSBs) might contribute to weight gain. The available evidence is insufficient to set an upper limit for sugars based on their effects on body weight.

- Type 2 diabetes: controversial findings on the association between total sugars and/or specific types of sugars and diabetes risk were reported in large prospective cohort studies. However positive associations were found between SSBs and increased type 2 diabetes risk. The available evidence was found insufficient to set a Tolerable Upper Level of Intake (UL) for sugars based on their effects on type 2 diabetes risk.
- Dental caries: available data do not allow the setting of a UL for (added) sugars on the basis of a risk reduction for dental caries, as caries development related to consumption of sucrose and other cariogenic carbohydrates does not depend only on the amount of sugar consumed, but it is also influenced by oral hygiene, exposure to fluoride, frequency of consumption and various other factors.

The NDA Panel concluded that the available data did not allow the setting of a UL for total or added sugars, neither an Adequate Intake (AI) nor a Reference Intake range (RI). However evidence on the relationship between patterns of consumption of sugar-containing foods and dental caries, weight gain and micronutrient intake should be considered when establishing nutrient goals for populations and recommendations for individuals and when developing food-based dietary guidelines (FBDG).

3. Terms of reference as provided by the mandate requestor

The request is for scientific assistance in line with Regulation (EC) No 178/2002 in assessing a DRV for added sugars, which would benefit risk managers and substantially support their work with dietary guidelines and nutrient recommendations if they could base their advices on an up-to-date assessment by EFSA.

To this end, EFSA has been requested to update its Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre published in 2010 (EFSA NDA Panel, 2010a), on the basis of the most recent scientific evidence, in order to derive a science-based cut-off value for a daily exposure to added sugars which is not associated with adverse health effects.

The mandate requestor clarified that the intake of interest is added sugars from all sources, i.e. sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup and other isolated sugar preparations used as such or added during food preparation and manufacturing. The health outcomes of interest are those already addressed in the EFSA 2010 opinion, i.e. micronutrient density of the diet, glucose tolerance and insulin sensitivity, serum lipids, other cardiovascular risk factors (blood pressure), body weight, type 2 diabetes and dental caries in adults and children.

To address this mandate, EFSA is requested to consider published reports from national and international bodies/authorities addressing the health effects of added sugars, as well as systematic reviews and meta-analysis published since 2010 on this topic.

4. Background information

To address this mandate EFSA is requested to consider, as background information and sources of data, published reports from national and international authorities/bodies addressing the health effects of sugars, as well as systematic reviews and meta-analysis published since 2010 on this topic.

An overview of the most recent existing DRVs and recommendations issued by other national and international authorities/bodies can be found in Appendix A. These publications will be used as sources of individual studies meeting the inclusion criteria for the present assessment through the scrutiny of their reference list.

A scoping literature search for systematic reviews and meta-analysis addressing the health effects of sugars or any of its dietary sources published in English since 2009 has also been performed. The list of the references identified and their main characteristics (e.g. exposure and endpoints of interest) can be found in Appendix B. These systematic reviews and meta-analysis will be used in two ways:

a) As sources of individual studies meeting the inclusion criteria for the present assessment through the scrutiny of their reference list;
b) As starting point for the literature searches to be carried out in the context of this assessment, whenever appropriate (see Section 9.2).

Data on the most recent national recommendations on sugars consumption in European countries will also be gathered through a questionnaire to National Competent Authorities (Appendix C).

5. Interpretation of the Terms of Reference

5.1. Definition of the exposure

Different terms and definitions have been used by researches and risk managers for dietary sugars. Among these:

i) *Sugars (total),* which are glycaemic carbohydrates composed of 1–2 monomers found in food. The main types of sugars found in mixed diets are the monosaccharides glucose, fructose and galactose, and the disaccharides sucrose, lactose, maltose and trehalose (FAO/WHO, 1998; EFSA NDA Panel, 2010a).
ii) *Added sugars*, which include sugars (mono- and disaccharides) used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table. This definition was first applied in the 2000 US Dietary Guidelines for Americans (USDA/HHS, 2000), and then by the IoM (2005), EFSA (EFSA NDA Panel, 2010a) and some European countries (Nordic Council of Ministers, 2014).
iii) *Free sugars*, which include monosaccharides (glucose, fructose and galactose) and disaccharides (sucrose, lactose, maltose and trehalose) added to foods by the manufacturer, cook, or consumer plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates. This term has been used by the World Health Organization (WHO, 2003, 2015).
iv) *Non-milk extrinsic (NME) sugars*, defined as sugars not located within the cellular structure of a food, such as those found in fruit juice, honey and syrups, and those added to processed foods, excluding lactose in milk. The term originated from the UK Department of Health (1989) as opposed to *intrinsic sugars*, which are those located within the cellular structure of a food (e.g. naturally found in fruits and vegetables). On its assessment of 2015, the UK Scientific Advisory Committee on Nutrition (SACN) (2015) adopted the WHO definition of *free sugars* to provide recommendations on sugar intakes.

This assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose) taken through the oral route only. Sugar alcohols (polyols), other substances used as sugar replacers and other mono- or disaccharides present in the diet in marginal amounts, are not included in the term 'sugars' for the purpose of this assessment.

To allow comparability with previous assessments done by EFSA and by other bodies, total sugars, added sugars and free sugars as defined above will be addressed in this protocol.

5.2. Objectives of the risk assessment

This mandate is a request for EFSA to update its Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre published in 2010 (EFSA NDA Panel, 2010a) with respect to (added) sugars, and therefore interpreted as a request in the context of establishing ULs for nutrients for the general European population. The principles for the application of risk assessment to nutrients in general, and for deriving ULs in particular, have been described elsewhere (SCF/EFSA NDA Panel, 2006; EFSA NDA Panel, 2010b).

EFSA interprets this mandate as a request to provide scientific advice on an UL for (total/added/free) sugars, i.e. the maximum level of total chronic daily intake of sugars (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. 'Tolerable intake' in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure.

ULs may be derived for various life stage groups in the population. The UL is not a recommended level of intake. If there are no, or insufficient, data on which to base the establishment of a UL, as it was the case in 2010 for total or added sugars (EFSA NDA Panel, 2010a), an indication should be given on the highest level of chronic daily intake (from all sources) where there is reasonable confidence in data on the absence of adverse effects (i.e. a science-based cut-off value for a daily exposure which is not associated with adverse health effects). If there are no, or insufficient, data on which to base the establishment of a UL or a cut-off value for (total/added/free) sugars from all sources because the evidence available relates to one or few sources only, or to a particular type of sugar (e.g. fructose, glucose, sucrose), and the extrapolation of the results to (total/added/free) sugars from all sources is found to be unjustified, scientific advice could be provided on quantitative

intakes in relation to one or few sugar sources only, and/or in relation to one type of sugar only (e.g. fructose, glucose, sucrose) (Figure 1).

The characterisation of the risk (SCF/EFSA NDA Panel, 2006) includes a description of the scientific uncertainties associated with the UL estimates in order to indicate the degree of scientific confidence that can be placed in these estimates. It will also include an estimate of intake for population groups as well as an indication of the margin between actual intakes and the UL, and an indication of circumstances, if any, in which risk is likely to arise. If a UL for (total/added/free) sugars cannot be established, other values could be used instead to characterise the risk (Figure 1).

It is out of the scope of this assessment to address possible beneficial health effects of sugars or of particular dietary sources of sugars.

The outcome of the assessment is expected to assist Member States and health professionals in establishing nutrient goals for populations and recommendations for individuals, and when developing FBDG.

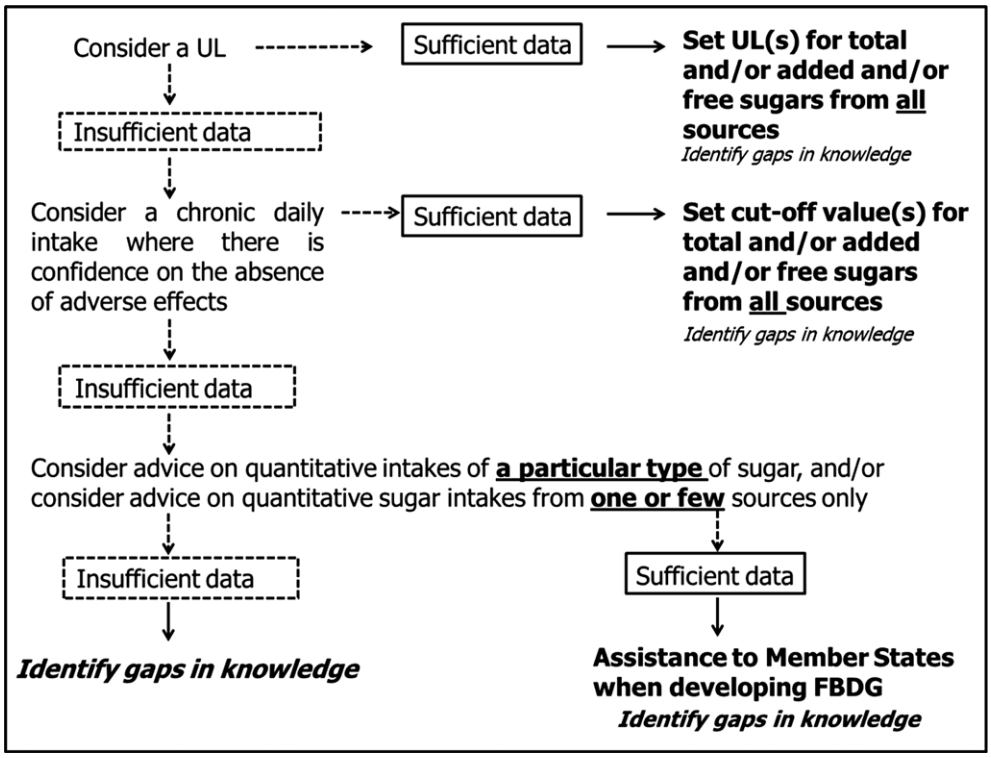


Figure 1: Step-wise process to provide scientific advice on total/added/free sugars

5.3. Target population

Adverse effects of nutrients are influenced by physiological changes and common conditions associated with growth and maturation that occur during an individual's lifespan. Therefore, where necessary, and to the extent possible, ULs are derived for each separate life-stage group, e.g. infants, children, adults, the elderly and women during pregnancy or lactation. Even within relatively homogenous life-stage groups, there is a range of sensitivities to adverse effects, e.g. sensitivity is influenced by body weight and lean body mass.

The derivation of ULs for the general population, divided into various life-stage groups, accounts for normally expected variability in sensitivity due to e.g. ethnicity, dietary habits, nutritional status, physical activity level (PAL) and metabolic risk profile. This includes individuals within the general population at risk of chronic disease (e.g. with excess body weight, elevated blood pressure, blood glucose and/or blood lipids but not on pharmacological treatment for the condition). It excludes, however, subpopulations with distinct vulnerabilities due to genetic predisposition or other considerations (e.g. individuals with inborn errors of carbohydrate metabolism) because including these would result in ULs which are significantly lower than are needed to protect most people against adverse effects of high intakes. Subpopulations needing special protection (e.g. individuals on

pharmacological treatment for obesity, diabetes, hypertension, dyslipidaemia, chronic liver or renal diseases) are better served through the use of public health screening, health care providers, or other individualised strategies.

The following groups will be considered *a priori*:

- Infants ≥ 4 to < 12 months
- Toddlers (young children) ≥ 1 to < 3 years
- Other children ≥ 3 to < 10 years
- Adolescents ≥ 10 to < 18 years
- Adults ≥ 18 to < 65 years
- Elderly adults ≥ 65 years
- Pregnant women

The age ranges may be modified by the NDA Panel depending on the available data, e.g. children may be further categorised according to the type of dentition (primary – milk or secondary – permanent) in relation to dental caries.

For this assessment, it is anticipated that lactating women will be considered together with other women in child-bearing age.

Infants < 4 months of age will be excluded from the assessment on the assumption that they are exclusively fed with breast milk or breast milk substitutes (EFSA NDA Panel, 2009).

5.4. Adverse effects and endpoints

The assessment will focus on possible adverse effects of sugars intake on endpoints selected based on the scope of the mandate, on previous assessments done by other bodies (Appendix A), on the systematic reviews available (Appendix B) and on the comments received through the public consultation (EFSA, 2018).

Both disease endpoints and other endpoints will be addressed. Disease endpoints are considered to be the most direct, or applicable, to the assessment. Other endpoints are relevant but less direct, and can include upstream indicators, risk factors, intermediate endpoints or measures related to disease endpoints.

The disease endpoints of interest are:

a) Incidence/severity of dental caries
b) Incidence of metabolic diseases:

   i) Obesity,
   ii) Type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM),
   iii) Hypertension,
   iv) Dyslipidaemia,
   v) Cardiovascular diseases (CVDs),
   vi) Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NAFLD and NASH),
   vii) Gout.

Other endpoints of interest are:

a) Measures of body fatness and body fat distribution; birth weight-related endpoints,
b) Ectopic fat deposition (e.g. muscle, liver),
c) Measures of glucose homoeostasis,
d) Blood pressure,
e) Blood lipids,
f) Uric acid,

The outcome variables that will be investigated in relation to the above-mentioned endpoints are depicted in Section 9.1.

6. Identification of the assessment subquestions

The identification of the assessment subquestions follows the principles of risk assessment for nutrients (SCF/EFSA NDA Panel, 2006). The assessment subquestions are illustrated in Table 1.

For **hazard identification**, human studies provide the most relevant data and, when they are of sufficient quality and extent, are given the greatest weight. Owing to the wealth of human studies

available on sugars intake and that extrapolation from animal models to humans is subject to considerable uncertainties, the Panel considers that evidence for adverse effects of sugars on humans should be obtained from human studies (**subquestions 4 and 5**).

Decisions on whether structural or functional alterations observed in human studies represent adverse effects or changes of little or self-limiting biological importance will be based on scientific judgement and will be taken on a case-by-case basis. In this context, it will be important to determine:

a) the causal significance of an exposure–effect association indicated by observational studies, primarily for disease endpoints. Criteria for judging this include demonstration of a temporal relationship, consistency, strength of association, a dose–response relationship (a biological gradient), specificity, biological plausibility and coherence; and
b) the clinical significance of an intake–effect relationship indicated by intervention studies primarily on other (than disease) endpoints. For energy-containing macronutrients, such as sugars, it will be important to determine how such relationships relate to energy-wise comparable intakes of other energy-containing macronutrients which are reasonably expected to replace the macronutrient under assessment in the diet. For sugars, the Panel considers that other glycaemic carbohydrates (e.g. starch) are the most appropriate comparison (EFSA NDA Panel, 2010a). Isocaloric comparisons with other macronutrients, however, may provide additional information which could be considered in the assessment.

Relevant experimental data (animal models, *in vitro* data) and knowledge of the molecular or cellular events underlying the adverse effect (mode of action) can assist in dealing with problems of data interpretation (**subquestion 6**).

Hazard characterisation includes a dose–response assessment which addresses the relationship between (total/added/free) sugars intake (dose) and adverse effect (in terms of intake and severity). Only human studies will be considered for that purpose (**subquestions 4 and 5**). The selection of the most appropriate or critical data set(s) for deriving the UL will be made on the basis of data quality, taking into account the related uncertainties and the possibility to derive quantitative estimates. Data on bioavailability (digestion, absorption and metabolism) will be considered to explain any apparent differences in dose response between different types, forms and sources of sugars (**subquestion 3**). Critical data set(s) should document the route of exposure and magnitude and duration of intake, and the intake that does not produce adverse effects as well as the intake which produces adverse effects. If more than one data set is found to be suitable and the UL that can be derived from each of them differs (e.g. for different disease endpoints), scientific advice will be provided for each of them separately. If there are no, or insufficient, data on which to base the establishment of a UL, an indication will be given on the highest level of intake of (total/added/free) sugars where there is reasonable confidence in data on the absence of adverse effects (Figure 1).

Risk characterisation includes a description of the scientific uncertainties associated with the UL estimates (or alternative estimates as the case may be; Figure 1) to indicate the degree of scientific confidence that can be placed in these estimates. Where data are available, it also includes an estimate of intake (from occurrence data and food consumption data; **subquestions 1 and 2**) for population groups as well as an indication of the margin between actual intakes and the UL, and an indication of circumstances, if any, in which risk is likely to arise.

Table 1: Assessment subquestions to be answered

Number	Subquestion
1	What are the levels of (total/added/free) sugars in foods and beverages in Europe?
2	What is the distribution of intakes of (total/added/free) sugars from all dietary sources (and by food source) by population group?
3	What are the digestion, absorption and metabolism of different types of sugars from different sources in humans?
4	What is the relationship between the intake of (total/added/free) sugars and metabolic diseases (disease endpoints and other endpoints) in the target population?
5	What is the relationship between the intake of (total/added/free sugars) and dental caries in the target population?
6	Which could be the potential mode(s) of action underlying the adverse effects (if any) of (total/added/free) sugars intake?

7. Methods to answer subquestions 1 and 2

7.1. Levels of sugars in foods and beverages in Europe

7.1.1. Development of a food composition database for total sugars

Since only total sugars are subject to mandatory labelling in Europe and there are no analytical methods to distinguish between added/free sugars and other sugars present in foods, available data on total sugars will be used as starting point to estimate the levels of added and free sugars in foods and beverages. To that end, a food composition database for total sugars will be developed first.

Data on total sugars will be extracted from the EFSA's food composition database, which was compiled as a deliverable of the procurement project 'Updated food composition database for nutrient intake' (Roe et al., 2013). The aim of the project was to provide EFSA with an updated food composition database covering approximately 1,750 food entries in the EFSA FoodEx2 classification system[1] with additional FoodEx2 facet descriptors, and to expand the data set to include harmonised information on the most common composite recipes of European countries and harmonised information on food supplements. In case no country-specific data were available for certain food codes, data compilers borrowed compatible data from other countries and/or from similar foods.

The EFSA's food composition database contains raw data for energy, macro- and micronutrients from national food composition databases up to 2012 provided by fourteen national food database compiler organisations. Within the EFSA's food composition database, 12 countries provided data on total sugars covering about 1290 FoodEx2 codes. The number of values for total sugars available for a given FoodEx2 code is variable.

For the purpose of this Scientific Opinion, a single European food composition database for total sugars will be developed from the information available in the national food composition databases. To that end, an outlier analysis will be performed to identify any value which deviates from the others for a given food code, which could be either wrongly attributed values (data cleaning) or values describing real variability in total sugars content. For food codes for which no outliers can be identified, the mean will be taken as a unique value.

The outlier assessment will prioritise foods with a high content of total sugars and foods largely consumed by one or more population subgroups. The expected variability in the total sugars content will decrease as the FoodEx2 level increases. Such variability will inform decisions regarding the level of FoodEx2 at which values for total sugars need to be attributed, together with data on the frequency of consumption gathered from the EFSA food consumption database. In this context, the Mintel Global New Products Database (GNPD),[2] an online database which monitors product introductions in consumer markets of packaged goods worldwide, will be used to check if the variability detected in the EFSA's food composition database regarding the total sugars content of manufactured foods reflects real variability of products in the market, and also to decide whether more than one scenario needs to be considered for risk characterisation regarding one or more food groups, and at which FoodEx2 level (i.e. whether two extreme values (lowest and highest), rather than a mean value, will need to be assigned to a food code to evaluate the impact of this variability on total sugars intake) (Figure 2).

A similar process has been undertaken to build the EFSA's food composition database for a number of vitamins and minerals in order to support EFSA's scientific opinions on DRVs for nutrients.

7.1.2. Development of food composition databases for added and free sugars

A European food composition database for added sugars in foods and beverages will be developed taking into account the 10-step methodology described by Louie et al. (2015) for added sugars and adapted by FSANZ[3] to determine the amount of added sugars in foods in the AUSNUT 2010–2013 food nutrient database. Although the definition of added sugars (a component of free sugars) in the

[1] https://www.efsa.europa.eu/en/data/data-standardisation

[2] The Mintel GNPD contains information on over two million food and beverage products, of which more than 800,000 are or have been available on the European food market. Mintel started covering European Union's food markets in 1996. Twenty out of the 28 EU member countries and Norway are present in the Mintel GNPD. The database provides the compulsory ingredient information presented in the labelling of products and the nutritional facts when available on the labels, which provide information about the use of sugars as ingredients and about the total sugar content of foods. http://www.mintel.com/global-new-products-database

[3] http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/foodnutrient/Pages/Determining-the-amount-of-added-sugars-and-free-sugars-in-foods-listed-in-the-AUSNUT-201113-dataset.aspx

Australian code includes maltodextrin and similar products, a decision was made by FSANZ not to capture these ingredients in the data set of added sugars (and therefore neither in the data set of free sugars) to maintain consistency with the definition of sugars used in nutrition labelling and with international food composition database practice where total sugars have been defined as being only mono- and di-saccharides. The same approach will be followed by EFSA for the same reasons.

The food composition database for added sugars will be developed for all FoodEx2 codes for which a consumption has been reported in the EFSA Comprehensive Food Consumption Database (see Section 7.2.1) in combination with the relevant FoodEx2 facet descriptors included in the EFSA FoodEx2 classification system (e.g. sugar free facet), using as starting point the food composition database for total sugars (Section 7.1.1). The step-wise methodology described by Kibblewhite et al. (2017) will be adapted to develop the food composition database for free sugars by applying the definition given in Section 5.1 of this protocol as strictly as possible. Databases for added and free sugars will be developed in close consultation with the mandate requestor (Figure 2). All the steps of the process will be thoroughly documented.

7.2. Estimates of intake of total, added and free sugars from all dietary sources

Estimates of intake of total, added and free sugars from all dietary sources will be obtained using data from the EFSA Comprehensive Food Consumption Database in combination with the food composition databases for total, added and free sugars (Sections 7.1.1 and 7.1.2).

7.2.1. The EFSA Comprehensive Food Consumption Database

Food consumption data from the EFSA Comprehensive Food Consumption Database (hereinafter referred as Comprehensive Database) will be used in order to assess the intake of free sugars. The Comprehensive Database provides a compilation of existing national information on food consumption at individual level. It was first established in 2010 (EFSA, 2011; Huybrechts et al., 2011; Merten et al., 2011). The latest version of the Comprehensive Database, updated on 26 April 2018, contains results from 61 different dietary surveys carried out in 25 different Member States.

Within the dietary surveys, subjects are classified in different age groups as follows:

1) Infants: 1–11 months old
2) Toddlers: ≥ 1 year to < 3 years old
3) Other children: ≥ 3 years to < 10 years old
4) Adolescents: ≥ 10 years to < 18 years old
5) Adults: ≥ 18 years to < 65 years old
6) Elderly: ≥ 65 years to < 75 years old
7) Very elderly: ≥ 75 years old

Data from infants 4 to 11 months old only will be considered in this assessment.

Overall, the Comprehensive Database is the most complete and detailed collection of food consumption data currently available in the EU. Consumption data were collected using single or repeated 24- or 48-h dietary recalls or dietary records covering from three to 7 days per subject. Surveys with only one observation day per subject, or which used food frequency questionnaires (FFQ) for data collection, were excluded. Owing to the differences in the methods used for data collection, direct country-to-country comparisons can be misleading. Detailed information on the different dietary surveys included in the Comprehensive Database is shown on the EFSA website,[4] including the number of subjects and days available for each age group. If new food consumption surveys become available during the assessment and up to December 2018, the most recent survey for a given country and age group will be used.

The linking between the foods consumed and the food composition databases for total, added and free sugars (Sections 7.1.1 and 7.1.2) will be done through the FoodEx2 system (EFSA, 2015b).

7.2.2. Sugars intake calculation

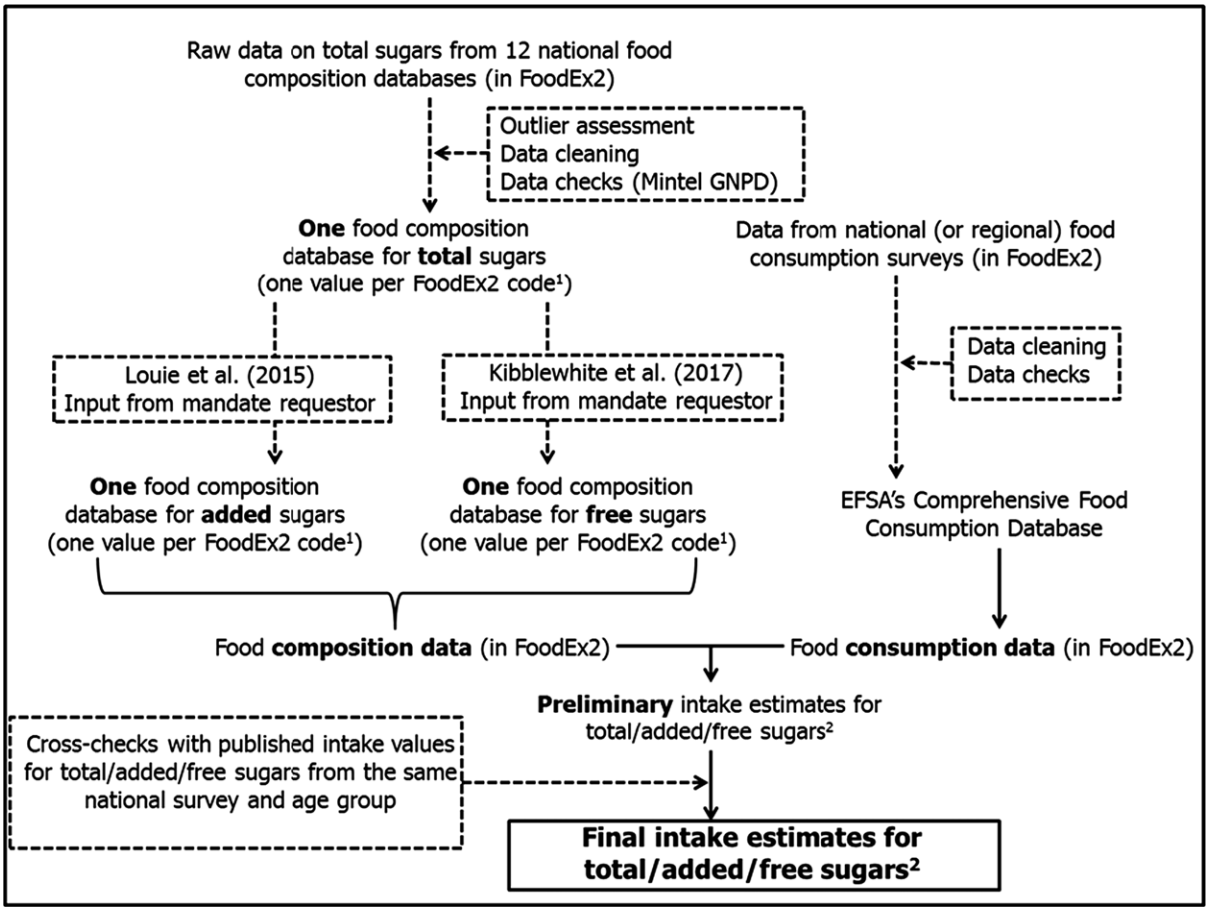
The intake of total/added/free sugars (in grams per day) will be calculated at individual level by multiplying the average daily consumption for each food or food group with the corresponding

[4] http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

concentration of total/added/free sugars, summing up the respective intakes throughout the diet. The intake of total/added/free sugars will also be expressed as percentage of total energy intake (%E) and as percentage of non-alcohol energy intake (non-alcohol E%). In line with the Guidance of EFSA for the Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment (EFSA, 2011), chronic total/added/free sugars intake calculations will be performed only for subjects with at least two reporting days. In this context, chronic total/added/free sugars intake refers to the arithmetic mean of all reporting days available for the same subject. The intake will be modelled using the SAS software (SAS Enterprise Guide 5.1, 2013). The mean as well as the 5th, 50th and 95th percentiles of intake will be derived for each survey and age group (and sex group, if appropriate), respectively. Data on the contribution of different food groups to (total/added/free) sugars intake by survey and age group will also be presented.

Different intake scenarios could be considered in the intake calculation process, especially if more than one value for total/added/free sugars is assigned to one or more FoodEx2 codes in the food composition database (Figure 2).

To evaluate the accuracy of the results obtained, these will be compared with published intake values for total/added/free sugars from the same survey data set and age group, whenever available. These data will be retrieved through a questionnaire to the National Competent Authorities of European countries (Appendix C).



Legend to Figure 2: 1) Two values for a given FoodEx2 code may be assigned when both the observed variability in sugars content and the frequency of consumption are high, so that different intake scenarios could be considered; 2) In grams per day and as E% per country and population group.

Figure 2: Steps that will be followed to estimate intakes of total, added and free sugars

8. Method to answer subquestion 3

In order to address the digestion, absorption and metabolism of different types of free sugars from different food matrices in humans, background information will be gathered by the WG experts and EFSA staff through a narrative review. Recent textbooks, authoritative reviews and research papers retrieved through searches in bibliographic databases, and selected on the basis of their relevance, will be used as sources of information.

9. Methods to answer subquestions 4 and 5

Subquestions 4 and 5 will be answered by performing systematic reviews and, possibly, dose–response meta-analyses if the available data allow doing so. The conceptual framework for the systematic reviews on sugars intake in relation to disease and other endpoints is shown in Figure 3.

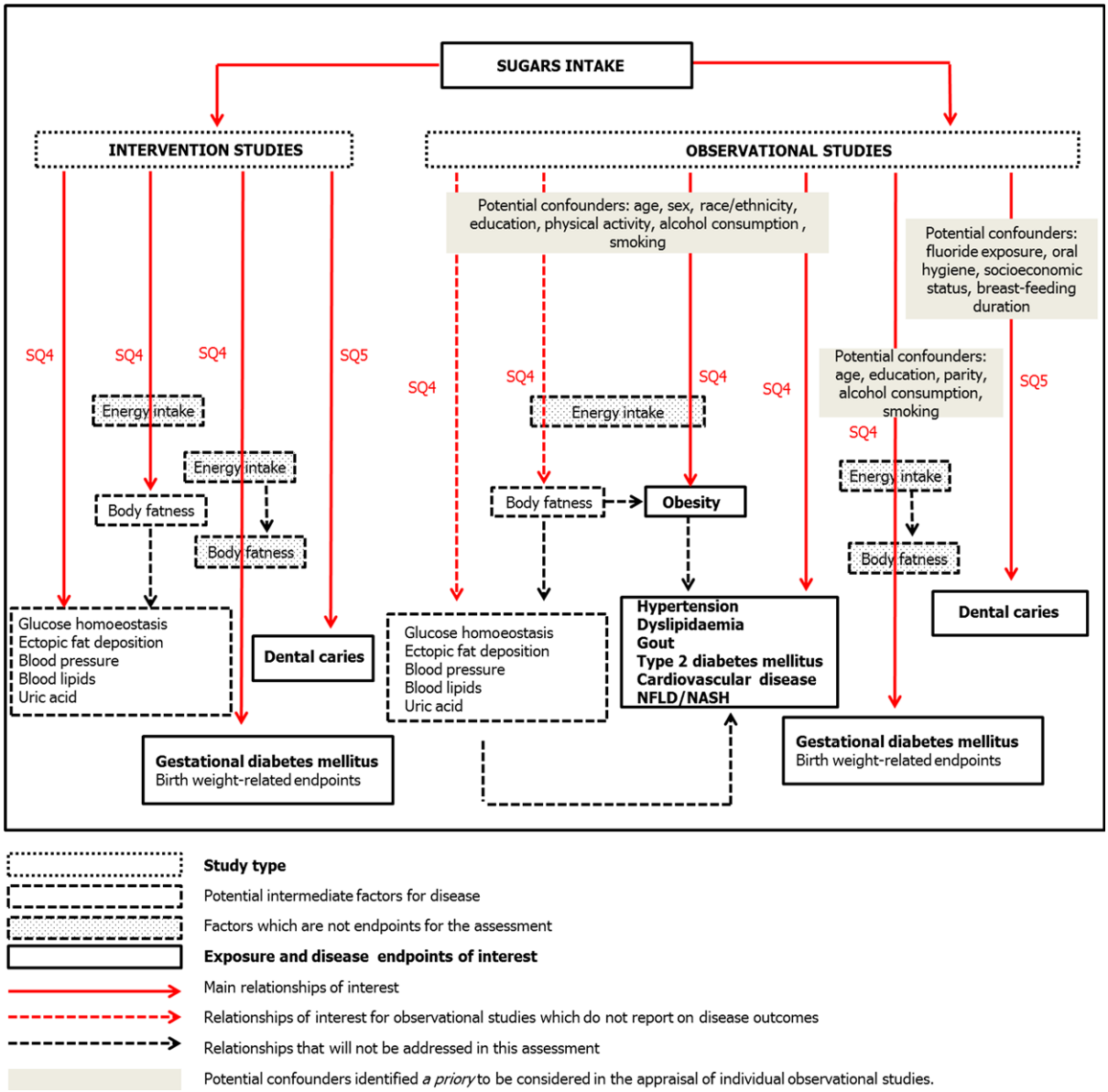


Figure 3: Conceptual framework for the systematic reviews on sugars intake in relation to disease endpoints and other endpoints

9.1. Eligibility criteria for study selection

The selection of human studies relevant to subquestions 4 and 5 will be performed using the eligibility criteria described in Table 2.

For subquestion 4, the minimum study duration for the inclusion of intervention studies has been selected by considering the time generally required for the stabilisation of the endpoints assessed following a nutritional intervention. The minimum study duration for the inclusion of observational studies for subquestion 4, and for the inclusion of intervention and observational studies for subquestion 5, is based on the minimum time estimated to be needed for the disease to develop in individuals free of the disease at baseline (expert judgement).

Regarding the study location, no limits are applied. It is acknowledged, however, that the background diet may affect the relationship between the intake of sugars and the endpoints being addressed, and that major differences in the background diet may limit the extrapolation of the results obtained outside Europe to the European population. This aspect will be considered when synthesising the evidence (Section 9.6).

Table 2: Eligibility criteria for human studies to address subquestions 4 and 5

INTERVENTION STUDIES		
Study design	In	Randomised controlled trials Non-randomised, comparative studies of interventions[(a)]
	Out	Single-arm intervention studies with no control group
Study duration	In	Depending on the endpoints addressed, as follows: Measures of body fatness ≥ 6 weeks Ectopic fat deposition ≥ 2 weeks Measures of glucose homoeostasis: ≥ 1 week to ≥ 12 weeks[(b)] Blood pressure, blood lipids and uric acid ≥ 4 weeks Dental caries: ≥ 1 year for primary dentition and ≥ 18 months for permanent dentition Pregnancy endpoints: any duration
	Out	Studies of shorter duration
Study location	In	Any location
Population	In	Adults (≥ 18 years) and children (4 months to < 18 years) from the general population, including overweight or obese subjects, subjects at risk of disease (e.g. with impaired glucose tolerance, impaired fasting glucose, NAFLD), and subjects with one or more features of the metabolic syndrome which are not on pharmacological treatment during the intervention
	Out	Studies targeting individuals with a disease (except for obesity), either untreated or under pharmacological/surgical treatment for the disease, or individuals on a therapeutic diet, including weight-loss diets Studies in individuals under physical training programs (e.g. athletes, military), except for dental caries
Intervention/control	In	Studies aiming at: – isocaloric exchanges of sugars with other glycaemic carbohydrates (e.g. starch) – isocaloric exchanges of sugars with macronutrients other than glycaemic carbohydrates (e.g. protein, fat) – isocaloric exchanges of different types of sugars (e.g. fructose vs glucose) – replacing sugar-containing foods with sugar-reduced or sugar-free foods (either under controlled or free-living conditions) – a quantitative change (increase, decrease) in sugars intake from one or more sources vs usual diet or no advice (either under controlled or free-living conditions)
	Out	Studies aiming at: – a quantitative change in sugars intake in the context of energy-restricted diets aiming at weight loss – studies not providing sufficient information to allow quantitative estimates of sugars intake, whether total or from one or more dietary sources (e.g. studies reporting only on the frequency of consumption of one or more dietary sources of sugars with unknown sugars content)

		– interventions targeting simultaneous changes in dietary/lifestyle factors other than the amount of sugars intake from one or more sources relative to the control group (e.g. advice on teeth brushing or physical exercise provided to the intervention or control group only)
Endpoints of interest	In	*Body fatness and ectopic fat deposition* – Measured body weight, BMI, waist circumference, sagittal diameter – Body fat measured by neutron activation analysis (NAA), imaging techniques (DXA, MRI, CT), hydrostatic weighing, or air displacement plethysmography. – VAT assessed by imaging techniques (CT, MRI) – Ectopic fat deposition in muscle or the liver assessed by CT, MRI, magnetic resonance spectroscopy (MRS) or in biopsies *Glucose homoeostasis* – Dynamic indices of insulin sensitivity and/or beta-cell function calculated from measures of plasma glucose, serum insulin and C-peptide (when available) during clamp tests (hyperinsulinaemic-euglycaemic, hyperglycaemic), frequently sampled intravenous glucose tolerance tests (FSIGT), standard oral glucose tolerance test (OGTT), the continuous infusion of glucose with model assessment (CIGMA), or insulin suppression tests – Fasting plasma glucose, fasting serum insulin and static indices of insulin sensitivity and/or beta-cell function thereof (e.g. HOMA, QUICKI) – Indices of blood glucose control (HbA1c, fructosamine) *Blood pressure* – SBP and DBP (point ambulatory or home BP, 24-h BP) *Blood lipids* – total-c, LDL-c, HDL-c, VLDL-c, TG, apoB100, apoA1 and ratios thereof *Liver* – NAFLD/NASH activity scores as defined by the authors *Uric acid* – Uric acid concentrations in blood *Dental caries* – Indices of dental caries measured by a trained observer *Pregnancy endpoints* – Birth-weight related endpoints (e.g. birth weight, small for gestational age, large for gestational age) as defined by the authors – Incidence of GDM as defined by the authors
	Out	– Self-reported body weight, BMI, waist circumference, sagittal diameter – Body composition assessed by BIA or skinfold thickness – Dental caries self-reported or reported by parents; other endpoints (e.g. amount of dental plaque; plaque pH) – Studies not including at least one of the endpoints listed above
Language	In	Full-text document in English
	Out	Articles with the full text in another language
Publication year	In	Up to March 2018
Publication type	In	Primary research studies (i.e. studies generating new data) reported in full-text articles Primary research studies reported in letters to editors if the information provided is sufficient to allow a scientific evaluation of the results Systematic reviews and meta-analyses[(c)]

	Out	Narrative reviews, expert opinions, editorials and letters to editors not reporting on primary data Meetings' abstracts and posters Conference proceedings PhD theses Grey literature
OBSERVATIONAL STUDIES		
Study design	In	Prospective, longitudinal, observational (prospective cohort and nested case-control) studies
	Out	Retrospective case–control studies Cross-sectional studies Ecological studies Case studies/case series
Study duration	In	≥ 18 months for dental caries for permanent dentition ≥ 1 year follow-up for all other disease endpoints, including dental caries for primary dentition Pregnancy endpoints: any duration
	Out	Studies with a shorter follow-up
Study location	In	Any location
Population	In	Adults (≥ 18 years) and children (4 months to < 18 years) from the general population Studies targeting individuals at risk of disease (e.g. with impaired glucose tolerance, impaired fasting glucose, the metabolic syndrome, overweight, NAFLD) not on pharmacological treatment for the condition Studies in which prevalent cases of the disease endpoint of interest at baseline were excluded for data analysis
	Out	Studies targeting individuals with a disease (except for obesity), either untreated or under dietary or pharmacological/surgical treatment for the disease Studies in which prevalent cases of the disease endpoint of interest at baseline were not excluded for data analysis
Exposure	In	– Studies comparing different levels of sugars intake from one or more sources – Studies providing sufficient information to allow quantitative estimates of sugars intake, whether total or from one or more dietary sources (e.g. in absolute amounts, as %E, as non-alcohol %E) *Eating conditions*: *ad libitum* *Method to quantify sugars intake (one or more of the following)*: – 24-h urinary excretion of fructose and sucrose – Food records (at least 2 reporting days) – Diet recalls (at least 2 reporting days) – Dietary history – FFQs – Dietary interview in combination with one or more of the above
	Out	– Studies not providing sufficient information to allow quantitative estimates of sugars intake, whether total or from one or more dietary sources (e.g. studies reporting only on the frequency of consumption of one or more dietary sources of sugars with unknown sugar content) *Eating conditions*: under dietary controlled conditions prior to the dietary intake assessment *Method to assess intake of sugars*: – Any other method
Endpoints of interest	In	*Disease endpoints*: – Incidence of obesity as defined by the authors – Incidence of T2DM as defined by the authors – Incidence of hypertension as defined by the authors

		– Incidence of dyslipidaemia as defined by the authors – Incidence of stroke [haemorrhagic (intracerebral, subarachnoid) and/or ischaemic; fatal and/or non-fatal] – Incidence of coronary heart disease (fatal and/or non-fatal) – Incidence of myocardial infarction (fatal and/or non-fatal) – Incidence of congestive heart failure – Incidence of cardiac death – Incidence of fatal and/or non-fatal cardiovascular events (composite endpoint) – Other endpoints of fatal and/or non-fatal cardiovascular events as defined by the authors – Incidence of NAFLD or NASH as defined by the authors – Incidence of non-alcoholic liver fibrosis/cirrhosis/liver failure as defined by the authors – Incidence of gout – Indices of dental caries measured by a trained observer *Other endpoints*: – Incidence of overweight/high waist circumference as defined by the authors – Incidence of impaired fasting glucose – Incidence of hyperuricaemia – Endpoints as defined above for human intervention studies – Self-reported body weight and related endpoints – Body fat assessed by skinfold thickness or BIA *Pregnancy endpoints*: – As defined above for human intervention studies
	Out	– Self-reported waist circumference – Overall mortality – Dental caries self-reported or reported by parents; other endpoints (e.g. amount of dental plaque; plaque pH) – Studies not reporting at least one of the endpoints listed above
Language	In	Full-text document in English
	Out	Articles with the full text in another language
Publication year	In	Up to March 2018
Publication type	In	Primary research studies (i.e. studies generating new data) reported in full-text articles Primary research studies reported in letters to editors if the information provided is sufficient to allow a scientific evaluation of the results Systematic reviews and meta-analyses(c)
	Out	Narrative reviews, expert opinions, editorials and letters to editors not reporting on primary data Meetings' abstracts and posters Conference proceedings PhD theses Grey literature

NAFLD: non-alcoholic fatty liver diseases; DXA: dual-energy X-ray absorptiometry; MRI: magnetic resonance imaging; CT: computed tomography; VAT: visceral adipose tissue; HOMA: homeostasis model assessment; QUICKI: Quantitative insulin sensitivity check index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; VLDL-c: very low-density lipoprotein cholesterol; GDM: gestational diabetes mellitus; BMI: body mass index; BIA: Bioelectrical impedance analysis; FFQ: Food frequency questionnaire; NASH: non-alcoholic steatohepatitis.

(a): Prospective studies that compare the effects of two or more interventions which did not use randomisation to allocate individuals or clusters to the comparison groups.

(b): For dynamic indices of insulin sensitivity and/or beta-cell function ≥ 1 week; for static indices and fructosamine ≥ 4 weeks; for HbA1c ≥ 12 weeks.

(c): Systematic reviews, including meta-analyses, on this topic that will be identified during the process of literature screening will be collected for the purpose of reviewing the reference list but will not be considered to contribute to the final number of studies considered eligible unless they also contain original data.

9.2. Literature searches for studies meeting the eligibility criteria

For subquestions 4 and 5, an extensive literature search will be performed in bibliographic databases. Sources of grey literature and databases of theses/dissertations will not be searched.

The bibliographic databases listed in Table 3 will be searched in order to identify relevant studies.

Table 3: Bibliographic databases to be searched for relevant studies

Database	Platform	Types of studies
Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley	Intervention studies
Cochrane Library. Cochrane Database of Systematic Reviews (CDSR)	Wiley	Systematic reviews
Cochrane Library. Database of Abstracts of Reviews of Effects	Wiley	Systematic reviews
Embase	Elsevier	Systematic reviews, intervention studies, observational studies
PubMed	NLM	Systematic reviews, intervention studies, observational studies
Scopus	Elsevier	Systematic reviews, intervention studies, observational studies

For subquestion 4, literature searches will be performed by type of endpoint. Previous systematic reviews with similar review questions, similar or broader inclusion criteria and appropriate search strategies were identified during the scoping searches (see Appendix B). Therefore, date limits will be applied to the searches for subquestion 4 (by endpoint) and subquestion 5 using these systematic reviews as starting point whenever possible (Table 4). Studies published before these dates will be retrieved by hand-searching the reference lists of the systematic reviews (Appendix B) and from existing reports by other authorities/bodies (Appendix A). No retrospective date limits will be applied for endpoints for which no existing systematic review can be taken as starting point.

Table 4: Date limits applied to the searches and systematic reviews used as sources of relevant studies

Subquestion	Endpoints	Date limit	Systematic review
4	Adipose tissue	Intervention and observational studies: December 2011	Te Morenga et al. (2013)
4	Blood pressure	Interventions: August 2013	Te Morenga et al. (2014)
		Observational studies: no date limit	
4	Blood lipids	Interventions: August 2013	Te Morenga et al. (2014)
		Observational studies: no date limit	
4	All other endpoints	Intervention and observational studies: no retrospective date limit	
5	Dental caries	Intervention and observational studies: November 2011	Moynihan and Kelly (2014)

Date limits might be changed should new systematic reviews on the topic be identified which are considered to adequately cover the relevant literature. Existing systematic reviews (Appendix B) with narrower inclusion criteria regarding either the exposure (e.g. limited to SSBs) or the study duration (e.g. (Sonestedt et al., 2012; SACN, 2015)) will be hand searched.

The search terms that will be used for the exposure and the various endpoints of interest are depicted in Appendix D. The specific search strategies for each database will be developed at a later stage. The performance of the search strings will be tested against the reference lists of the systematic reviews shown in Appendix B.

The output from the searched databases, including all indexed fields per hit (e.g. title, authors, abstract), will be exported into separate Endnote® files, allowing a count of the individual hits per database. All the studies included in the above-mentioned systematic reviews will be added to specific Endnote® libraries. Files will then be combined and duplicate records will be removed.

The files obtained will be transferred into DistillerSR® Web-Based Systematic Review Software (Evidence Partners, Ottawa, Canada) for the selection procedure (see Section 9.3).

9.3. Study selection process

The whole selection process will be performed with DistillerSR®. Studies to be included in the review will be selected using a two-step selection procedure:

1) **Screening of title and abstract** to identify potentially relevant studies that will be included for full-text screening, applying the selection criteria described in Section 9.1. If the information contained in the title or abstract is not relevant to the research objectives, the article will not be selected for full-text assessment. During the screening process, studies will be categorised into two groups corresponding to the two subquestions that are the objectives of these systematic reviews.
This step will be conducted by WG experts and/or EFSA staff in duplicate, and by using machine learning techniques where/when appropriate. The results of the use of machine learning will be evaluated by a reviewer and documented. If the title and/or abstract do not mention the endpoints of interest for the assessment, but the words 'adverse effects' or 'side effects' are mentioned, the paper will be included to check if these effects have any relation to the endpoints of interest. If there are doubts or divergences which cannot be resolved between the two reviewers, the full article will be screened.

2) **Screening of full text** to assess if the article is relevant to the risk assessment.
This step will be conducted by WG experts and/or EFSA staff, in duplicate, for the references retrieved. Possible divergences will be discussed by the whole WG on sugars, in case these would highlight the need for amendments to the inclusion/exclusion criteria. The content of the full text will be checked against the inclusion and exclusion criteria established in the protocol.

Possible divergences or doubt for inclusion of domain-specific articles will be discussed together with the relevant expert from the WG, also in case these would highlight the need for amendments to the inclusion/exclusion criteria.

Articles reporting solely on digestion, absorption or metabolism (i.e. without reporting on the endpoints of interest), or reporting only on endpoints other than those listed in Section 9.1, will not be included in this research subquestions but will be flagged for subquestions 3 and 6, where appropriate.

Screeners will be trained using written documentation on study eligibility. Eligibility criteria will be pilot tested on a subset of records, and refined if prone to misinterpretation. The results of the different phases of the study selection process will be reported in a flowchart as recommended in the PRISMA statement on preferred reporting items for systematic reviews and meta-analyses (Moher et al., 2009).

9.4. Data extraction from included studies

Data will be extracted from the studies using predefined forms that comprise data on the characteristics of the studies (e.g. study design), their key-elements (e.g. population, intervention/exposure, comparator, outcomes (endpoints), setting and duration), results, aspects related to the internal validity of the studies (e.g. confounders, randomisation) and funding source.

Studies for which the information provided in the publication(s) does not allow a full scientific evaluation by the WG experts (e.g. studies with missing or ambiguous information) will be excluded at this step. The reasons for exclusion will be clearly indicated.

The data will be extracted in the original units of measurement, which will be subsequently harmonised to allow data analysis. The authors may be contacted to retrieve additional data if needed.

Regarding the intervention/exposure, data on the food source(s) of sugars, on the type of sugars consumed (e.g. fructose, glucose, sucrose) and on the frequency of sugars consumption will be extracted from the included studies whenever available. For observational studies, data on disease endpoints (dichotomous variables, i.e. incidence of hypertension, incidence of type 2 diabetes) will be extracted first whenever available. Data on other endpoints (continuous variables, e.g. blood pressure, fasting glucose) will only be extracted if data on corresponding disease endpoints are not reported (Figure 3).

If a full-text document reports on more than one study, the individual studies will be identified at this step to allow for data extraction at individual study level. If a single study is reported in more than one publication, different publications reporting on the same study (e.g. on different outcomes

(endpoints), at different time points) will be identified at this step. Data will be extracted for the last observation available for each endpoint (corresponding to the longest intervention or follow-up) for data analysis. Exceptions to this rule will be duly justified (e.g. on the basis of attrition and sample size, compliance with the intervention, other factors).

Clear instructions for extracting data will be developed. The data extraction forms will be created in DistillerSR® (Evidence Partners, Ottawa, Canada) and/or Excel, and pilot tested on a subset of studies. The piloting will also be used to identify sources of contextual (i.e. related to the key elements of the studies) heterogeneity. The forms and instructions will be refined if needed.

Data will be extracted from each individual study by one EFSA staff or one WG expert. In the piloting phase, extracted data will be validated by another EFSA staff or WG expert, in order to identify sources of possible errors. The data extraction will be then conducted by one EFSA staff/WG expert. Data quality checks will be performed for each study (Section 9.6).

9.5. Appraisal of the internal validity of the included studies

The risk of bias (RoB) of a given study in relation to a specific outcome (endpoint) refers to the risk of systematic errors in the design, recruitment, data collection or analysis that results in a mistaken estimation of the true effect of the exposure on the outcome.

The internal validity or RoB of each individual study included in the assessment will be appraised using a customised version of the OHAT/NTP RoB tool, which is suitable for both intervention and observational studies.[5] This tool was developed based on guidance from the Agency for Healthcare Research and Quality (Viswanathan et al., 2012), the Cochrane risk-of-bias tool for non-randomised studies of interventions (Sterne et al., 2014), the Cochrane Handbook (Higgins and Green, 2011), CLARITY Group at McMaster University (CLARITY, 2013) and other sources. The OHAT/NTP RoB tool was developed to provide a parallel approach to the evaluation of the RoB in the context of hazard identification for human risk assessment of chemicals, and to facilitate consideration of RoB across evidence streams (i.e. human, animal and mechanistic studies) with common terms and categories for RoB rating. For this assessment, the use of the tool will be limited to the aspects relevant to intervention and prospective observational studies in humans.

For each study, the appraisal will be done at outcome level, because for the same study the design and conduct may affect the RoB differently depending on the endpoints measured. Each study will be appraised by two independent experts from the WG ('the reviewers'). Possible discrepancies will be discussed by the whole WG. If upon further discussion the WG cannot reach an agreement on a RoB rating for a particular domain, the more conservative judgment (the highest RoB) will be selected.

The OHAT/NTP RoB tool outlines 10 RoB questions, grouped in 6 bias domains (selection, confounding, performance, attrition/exclusion, detection and selective reporting) - plus 'other sources of bias' -, which help identify the practices that may introduce bias (Table 5). Each RoB question addresses aspects relevant to specific study designs, i.e. 8 questions apply to intervention studies and 7 questions apply to prospective observational (cohort and nested case–control) studies (Table 5). Reviewers are required to answer RoB questions by applying a 4-level rating scale (Figure 4).

The RoB questions and rating instructions provided in the tool will be tailored to the specific subquestions illustrated in this protocol.

Table 5: Extracted from OHAT/NTP RoB tool (source: OHAT Handbook – 9 January 2015)[(a)]

Bias Domains and Questions	Controlled intervention*	Observational
Selection Bias		
1. Was administered dose or exposure level adequately randomized?	**X**	
2. Was allocation to study groups adequately concealed?	**X**	
3. Did selection of study participants result in appropriate comparison groups?		**X**
Confounding Bias		
4. Did the study design or analysis account for important confounding and modifying variables?		**X**

[5] https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

Bias Domains and Questions	Controlled intervention*	Observational
Performance Bias		
5. Were the research personnel and human subjects blinded to the study group during the study?	X	
Attrition/Exclusion Bias		
6. Were outcome data complete without attrition or exclusion from analysis?	X	X
Detection Bias		
7. Can we be confident in the exposure characterization?	X	X
8. Can we be confident in the outcome assessment?	X	X
Selective Reporting Bias		
9. Were all measured endpoints reported?	X	X
Other Sources of Bias		
10. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate and researchers adhered to the study protocol)?	X	X

*: Includes studies in humans with a controlled exposure including randomised controlled trials and non-randomised intervention studies.
(a): https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf

++	**Definitely Low** risk of bias	There is direct evidence of low risk-of-bias practices (May include specific examples of relevant low risk-of-bias practices)
+	**Probably Low** risk of bias	There is indirect evidence of low risk-of bias practices OR it is deemed that deviations of low risk-of bias practices for these criteria during the study would not appreciably bias results, including consideration of direction and magnitude of bias
-/NR	**Probably High** risk of bias	There is indirect evidence of high risk-of-bias practices OR there is insufficient information (e.g. not reported or "NR") provided about relevant risk-of bias practices
--	**Definitely High** risk of bias	There is direct evidence of high risk-of-bias practices (May include specific examples of relevant high risk-of-bias practices)

Figure 4: Answer format for the RoB questions (source: OHAT/NTP RoB tool)[5]

The OHAT/NTP RoB tool encourages judging the direction of bias, when possible. Empirical evidence about the direction of bias is discussed for each of the RoB questions. If there is no clear rationale for judging the likely direction of bias, reviewers are invited to simply outline the evidence and not to attempt a guess. This approach will be followed.

Once customised, the tool will be created in the review management software DistillerSR® to allow web-based appraisal of the studies.

Specific elements identified *a priori* and that will be considered in the assessment of confounding and biases related to the exposure and outcome characterisation are discussed below.

9.5.1. Consideration of potential confounders

When assessing the RoB of studies concerned with causality (e.g. which investigate the effect of an exposure on disease), confounding should be addressed regardless of the study design. When present, confounding may lead to a biased estimate of the effect of exposure on disease, either closer to the null (resulting in underestimation of the exposure effect) or departing from the null, and can even reverse the apparent direction of the effect.

There are several requirements for a factor to actually act as a confounder, as described by McNamee (McNamee, 2003) and illustrated below. The factor must:

1) be a cause of the disease, or a surrogate measure of the cause, in unexposed people; factors satisfying this condition are called 'risk factors'; and

2) be correlated, positively or negatively, with exposure in the study populations. If the study population is classified into exposed and unexposed groups, this means that the factor has a different distribution (prevalence) in the two groups; and
3) not be affected by the exposure. When a factor is an intermediate factor in the relationship between the exposure and the disease, it is affected by both the exposure and the disease, or shares a common cause with the disease which is in turn affected by the exposure, such factor cannot be considered a confounder.

Whereas criteria 1 and 3 can be judged based on current (expert) knowledge of external empirical evidence (e.g. prior research), criteria 2 can only be judged from internal evidence (i.e. evidence from the study under evaluation with respect to the RoB). Therefore, whether potential confounders identified *a priori* on the basis on current knowledge can actually confound the association between exposure and disease in a particular study by making the study groups not comparable in terms of disease risk is to be addressed on a case-by-case basis, in the context of each particular study.

The OHAT/NTP RoB tool does not include a separate question for confounding in human intervention studies because randomisation and allocation concealment should adequately address the issue of confounding. It recognises, however, that in some cases appropriate procedures for randomisation and allocation concealment may fail in accounting for confounding. For example, in the context of this assessment, confounding could be a concern if there are important differences among study groups in baseline characteristics which are risk factors for the outcome (endpoint) but not affected by the exposure (e.g. age, sex, PAL). In accordance with the OHAT/NTP guidance, for intervention studies where confounding is strongly suspected despite the fact that randomisation and allocation concealment are rated at 'probably low' or 'definitely low risk of bias', confounding will be addressed under 'other potential threats to internal validity' (OHAT/NTP, 2015).

In observational studies, potential confounding can be reduced by good design and appropriate statistical analysis (control for measured confounders), although it is acknowledged that the problem of confounding cannot be resolved fully in non-randomised designs. The aim of controlling for confounders in observational studies is to allow comparability of the study groups for the risk of disease which is not affected by the exposure, so that any observed difference in risk among groups can be attributed to differences in the exposure of interest.

Being sugars an energy-containing nutrient, an increase in energy intake and/or an increase in body fatness could be considered intermediate factors in the causal pathway between high sugars intake and adverse effects related to glucose homoeostasis, ectopic fat deposition, blood pressure, blood lipids and uric acid, which in turn could mediate the effect of high sugars intake on the incidence of hypertension, dyslipidaemia, gout, T2DM mellitus, CVD and NFLD/NASH (Figure 3). An increase in energy intake and/or an increase in body fatness could also be considered intermediate factors in the causal pathway between high sugars intake and adverse pregnancy outcomes (endpoints). All these intermediate factors could potentially be affected by the exposure and therefore do not meet the criteria to be considered as confounders (McNamee, 2003), but rather as a potential source of over-adjustment bias. The extent to which an effect of sugars intake on the endpoints of interest (except obesity and dental caries) may be mediated by changes in energy intake and/or body fatness will be explored in the synthesis of the evidence (Section 9.6). In addition, there are dietary factors known to be risk factors for one or more of the above-mentioned diseases, such the intake of sodium, potassium, saturated and *trans* fatty acids, or dietary fibre. However, these may or may not be associated with both the exposure and the endpoint within a given study, and therefore, they will be not considered as potential confounders *a priori*, but rather in the context of individual studies.

Based on recent publications, the Panel identified *a priori* an indicative list of potential factors that could confound the relationship between the intake of sugars and measures of body fatness, ectopic fat deposition, glucose homoeostasis, blood lipids, blood pressure and uric acid, and the relationship between the intake of sugars and incidence of overweight/obesity, hypertension, dyslipidaemia, gout, T2DM, cardiovascular disease and liver disease: age, sex, race/ethnicity, education (or education of the parents for studies in children), smoking habits, physical activity, alcohol consumption.

The Panel also identified *a priori* an indicative list of potential factors that could confound the relationship between the intake of sugars and dental caries: fluoride exposure (e.g. water fluoride, use of fluoride toothpaste, supplements), oral hygiene practices, socioeconomic status and breast feeding duration for studies on young children. Frequency of sugars consumption has been highly correlated to the amount of sugars consumed in observational studies and it is likely to be affected by the exposure, so that it will not be considered as a potential confounder in observational studies in relation to dental caries.

As for pregnancy outcomes, the Panel identified *a priori* the following factors that could potentially confound the relationship between the intake of sugars and birthweight-related endpoints or the incidence of GDM: parity, maternal age, education, alcohol consumption and smoking.

When assessing RoB in observational studies, the reviewers will consider, for each study, whether these factors can confound the association on a case-by-case basis. Additional confounders may be identified by the reviewers. The reviewers will consider whether the confounding variables were measured reliably and consistently within each study and whether the design and/or the data analysis adequately accounted for potential confounding (e.g. multivariable analysis, stratification).

9.5.2. Confidence in the exposure characterisation

The exposure of interest for the assessment is the daily intake of total/added/free sugars from all dietary sources. It is acknowledged however, that few of the available individual studies investigating the health effects of dietary sugars may have used the definition of added or free sugars as described in this protocol (Section 5.1) to characterise the intervention/exposure. In this context, the confidence in the exposure characterisation that will be assessed in relation to the RoB of individual studies refers to the confidence on the quantitative estimates for the sugar fraction that is being investigated in the study, and not the extent to which the exposure investigated on each study reflects the intake of total/added/free sugars from all dietary sources as defined in this protocol. The latter aspect will be discussed when integrating and weighing the evidence in light of the identified uncertainties to provide scientific advice on total/added/free sugars (see Figure 1 and Section 12).

In assessing RoB, reviewers will consider the risk of errors in the estimate of sugar intake for individuals and related risks of misclassification of individuals according to their exposure. The accuracy of sugar intake estimates may be affected by (i) the method (or combination of methods) used to assess the sugar fraction of interest for the study (e.g. 24-h urinary excretion of fructose and sucrose vs dietary records vs diet recalls vs FFQs; specificity of FFQs for the exposure of interest; validation; number of days recorded); (ii) the accuracy of 24-h urine collections and the accuracy of reporting dietary intakes (e.g. self vs dietitian assisted compilation of FFQs); (iii) systematic changes in habitual diet prior to the intake assessment. The reviewers will consider the resulting risk of misclassification in appraising the studies.

9.5.3. Confidence in the outcome assessment

Confidence in the outcome (endpoint) requires valid, reliable and sensitive methods to assess the outcome applied consistently across groups (OHAT/NTP, 2015). Outcome misclassification or measurement error may be unrelated to the exposure (non-differential) or related to the exposure (differential).

Factors that will be considered by the reviewers while assessing bias in relation to the outcome assessment include: (1) the objectivity of the outcome assessment, (2) the consistency in measurement of endpoints, and (3) the blinding of the outcome assessors (for knowledge of the exposure) (OHAT/NTP, 2015).

9.5.4. Summarising the internal validity of each individual study

Each study will be reported using a tabular summary form which will include the key elements of the study and a summary of the results of the critical appraisal.

When all the studies have been summarised in this way, the WG will consider whether and how to combine the scores from the RoB questions at the level of individual studies. The WG may consider using an algorithm to combine the scores in a weighted or unweighted manner: if so, the rationale for the chosen algorithm will be documented. Alternatively, the RoB scores may be kept separate for each RoB question and taken into account in the synthesis of evidence. The results of the RoB assessment will be taken into account in the weight of evidence assessment and uncertainty analysis (Sections 11 and 12).

9.6. Synthesis of the evidence

Data from included individual studies will be considered separately for each of study design and for each endpoint to derive single lines of evidence (Figure 3).

Information on inclusion criteria, RoB assessment and endpoints as extracted from the individual studies will be summarised in evidence tables. Data quality checks will be performed for each study. For each variable, the proportion of missing observations will be assessed; range checks will be carried out for all included variables to ensure that all values are reasonable; categorical variables will be

tabulated and key variables will be cross-tabulated to check for internal consistency. For intervention studies, results from intention-to-treat analyses will be preferred over per-protocol analyses if both are reported. In the case of missing data, flexible and transparent strategies will be pursued, such as requesting missing data from the authors, re-doing the analysis or placing the original results in adequate context according to the feasibility and adequacy of these approaches on a per-study basis. Effect estimates such as relative risks and odds ratios for dichotomous variables for disease endpoints, and differences in means for continuous variables for other endpoints along with measures of their statistical precision (usually 95% confidence intervals) will be extracted from the studies and reported in the assessment.

Whenever data allow for a meaningful quantitative synthesis of the evidence, effect estimates from intervention studies (for all endpoints; by study design) and observational studies (for disease endpoints) will be pooled separately and assessed through meta-analysis and dose–response meta-analysis, using fixed- and random-effects models as appropriate (Orsini et al., 2012; Crippa and Orsini, 2016; Discacciati et al., 2017). Dose–response meta-analysis is a statistical technique that aims to characterise the smooth and gradual change in non-linear responses along the range of a quantitative exposure using aggregated data from several studies. Within intervention studies, effect estimates will be pooled separately by study design (e.g. isocaloric exchange of sugars with other macronutrients, changes in sugars intake under free-living conditions). For observational studies, the suitability of unadjusted and adjusted models will be considered case-by-case for data analysis depending on the level of control for potential confounders and the risk of over-adjustment bias.

In addition to the meta-analyses stratified by study design, subgroup/stratified analyses will be performed according to age, gender, changes in body fatness (except for obesity and dental caries), type of dentition (for dental caries), type of sugar/food source/frequency of consumption, country or continent, and other factors suspected or known to modify the association between sugars intake and the endpoints assessed. Subgroup and sensitivity analyses will also be performed according to the RoB of the included studies, the degree of control for confounding, the methodology and quality of the exposure assessment, duration of follow-up for both the intervention and the observational studies, and possibly by the source of study funding. If needed, sensitivity analyses will be performed to evaluate the robustness of the findings and the possible influence of different biases on the summary pooled effect estimates (Arah et al., 2008; Rothman et al., 2012; Corbin et al., 2017). Influence analysis will be carried out by examining whether removal of single studies influences the results of the meta-analyses, and the reasons underlying such an influence on the effect estimates, if any (Rothman et al., 2012).

Statistical heterogeneity across study-specific findings will be taken into account in the statistical model and evaluated by visual inspection of forest plots and the I2 statistic (Higgins and Thompson, 2002; Higgins et al., 2003), and an attempt will be made to identify its sources.

The possibility of publication bias will be investigated using one or more of the following approaches: (a) visual inspection of funnel plots to investigate the association between study size and effect size (Altman, 1986); (b) Egger's regression test (Egger et al., 1997; Sterne and Egger, 2005); and (c) trim-and-fill analysis (Duval and Tweedie, 2004; Rothstein et al., 2005) following the approach of Peters Jaime et al. (2007).

If there are studies that are relevant but cannot be included in meta-analyses (e.g. due to differences in study design), their contribution to the assessment will be integrated with the results of the meta-analysis by a weight of evidence approach (Section 11). If none of the relevant studies for an effect are suitable for meta-analysis, evidence synthesis for that effect will be performed by a weight of evidence approach (Section 11).

9.7. Plans for updating the literature searches and dealing with newly available evidence

The literature searches performed as detailed above (Section 9.2) will be repeated approximately 3 months before the planned date of endorsement of the draft opinion by the Panel. Databases and keywords will be those of the original searches. Date limits will be defined based on the cut-off date of the preceding searches. The papers retrieved by these additional searches will be screened for relevance applying the same criteria.

Relevant studies will be reviewed by the WG experts and their contribution to the assessment will be integrated (with the results of a meta-analysis or otherwise) by a weight of evidence approach (Section 11), but will not be considered for inclusion in any meta-analysis.

10. Methods to answer subquestion 6

In order to address the mode(s) of action for possible adverse health effects of (total/added/free) sugars identified in subquestions 4 and 5, background information will be gathered by the WG experts and EFSA staff through a narrative review. Recent textbooks, authoritative reviews and research papers retrieved through searches in bibliographic databases, and selected on the basis of their relevance, will be used as sources of information. Articles reporting solely on digestion, absorption or metabolism that are identified/retrieved during the screening of the full text in the context of the systematic reviews described in Section 9 will also be considered, where appropriate. The mode of action by which sugars can contribute to the development of dental caries (subquestion 5), however, is considered to be well known.

11. Methods for integrating and weighing the evidence to set a UL for sugars

Integration of evidence will be performed at a number of levels and by different methods, according to what is appropriate given the available evidence (Figure 5). For subquestions 4 and 5, the following integration steps may be needed:

- Where appropriate, different studies (by study design) for the same endpoint will be combined by meta-analysis.
- Results from meta-analysis will be integrated with evidence from other relevant studies on the same endpoint (if there are any that could not be included in the meta-analysis) by a weight of evidence approach.
- For endpoints where meta-analysis is not feasible, relevant studies will be integrated by a weight of evidence approach.
- Where appropriate, results for different endpoints of the same type (e.g. disease and other endpoints relating to the same chronic disease) may be integrated by a weight of evidence approach.

The outcome of subquestions 4 and 5 will be integrated with the endpoints of subquestions 3 and 6 by a weight of evidence approach. The results of this will form the Panel's conclusions on the levels of intake for total/added/free sugars (UL or otherwise; Figure 1): this may result in more than one level of intake, depending on whether there is material variation between sugar fraction, effects and/or population groups.

The results of subquestion 1 (levels of total/added/free sugars in foods and beverages) will be integrated by calculation with food consumption data to address subquestion 2, resulting in intake assessments for the European population.

Risk characterisation will be performed by comparing results of the intake assessment (from subquestions 1 and 2) with the levels of intake (UL or otherwise; Figure 1) for total/added/free sugars (from subquestions 3, 4, 5 and 6) (Figure 5).

In several of the steps described above, integration will be performed by a weight of evidence approach using expert judgement. The methods will vary, depending on the evidence to be integrated and the specific considerations involved. In each case, the principles of EFSA's guidance on weight of evidence will be applied (EFSA Scientific Committee, 2017). Evidence will be organised into lines of evidence, where helpful. Relevance, reliability (including the RoB evaluations described in earlier sections) and consistency will be taken into account when weighing the evidence. Formal (EFSA, 2014) or semi-formal (EFSA Scientific Committee, 2018) methods for expert knowledge elicitation (EKE) will be used where appropriate. Detailed protocols will be established for each stage of the weight of evidence process before it is performed. Each stage of the process will be documented, including the reasons for any deviations from the protocol.

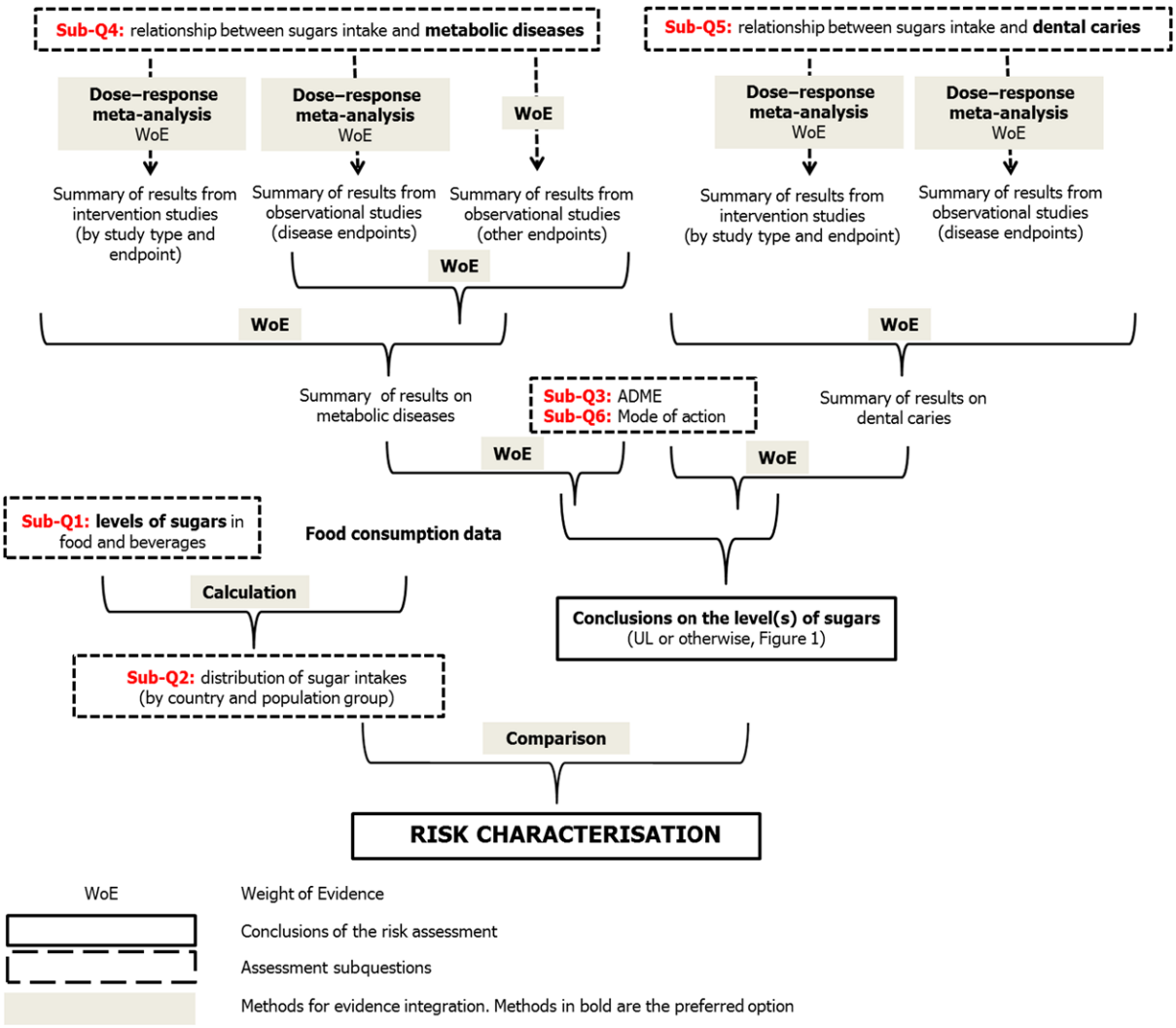


Figure 5: Conceptual framework for evidence integration

12. Evaluating the uncertainty in the body of evidence

Uncertainties in the estimates of total/added/free sugar intake in European countries may arise from inaccuracies in mapping food consumption data according to the FoodEx2 classification, from analytical errors or from errors in estimating the levels of total sugars in the national food composition tables, from errors in attributing levels of added/free sugars to foods from their content of total sugars, and from replacing missing values by values of similar food groups in the added/free sugars intake estimation process. These uncertainties may, in principle, result in both too high and too low estimates of total/added/free sugars intake.

For disease and other endpoints, once the individual studies are appraised for internal validity and after synthesising the evidence for each endpoint, line of evidence (i.e. intervention studies separately from observational studies; intervention studies by design) and subquestion, the uncertainties in the body of evidence will be identified, including factors such as the consistency of results, the precision of effect/association estimates and/or dose–response models, the internal and external validity (directness, generalisability, applicability) of the included studies, and gaps in knowledge.

Uncertainty analysis will be performed following approaches recommended by EFSA (EFSA Scientific Committee et al., 2018) for case-specific assessments. Uncertainty affecting each subquestion will be identified, and taken into account when evaluating the overall uncertainty for the main endpoints of the assessment: UL for the intake of total/added/free sugars (or otherwise; Figure 1) and risk characterisation. The overall uncertainty will be evaluated by expert judgement using either formal or semi-formal EKE methods (EFSA, 2014; EFSA Scientific Committee, 2018). For the UL of total/added/

free sugars (or otherwise; Figure 1), the weight of evidence (Section 11) and uncertainty analysis may be addressed together in a single EKE procedure. Detailed protocols cannot be specified in advance, but will be established for each stage of the uncertainty analysis before it is performed. Each stage of the process will be documented, including the reasons for any deviations from the protocol.

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Abbreviations

AHA	American Heart Association
AI	adequate intake
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
AUSNUT	Australian food and nutrient database
BIA	bioelectrical impedance analysis
BMI	body mass index
BP	blood pressure
CHD	coronary heart disease
CIGMA	Continuous infusion of glucose with model assessment
CT	computed tomography
CVD	cardiovascular disease
DRV	dietary reference value
DBP	diastolic blood pressure
DXA	dual-energy X-ray absorptiometry
EKE	expert knowledge elicitation

ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
FBDG	food-based dietary guidelines
FFQ	food frequency questionnaire
FoodEx2	Standardised food classification and description system developed by EFSA
FSANZ	Food Standards Australia New Zealand
FSIGT	Frequently sampled intravenous glucose tolerance tests
GNPD	Global New Products Database
GNS	German Nutrition Society
HDL-c	high-density lipoprotein cholesterol
HFCS	high-fructose corn syrups
HOMA	homeostasis model assessment
IoM	Institute of Medicine
LDL-c	low-density lipoprotein cholesterol
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAFLD	non-alcoholic fatty liver diseases
NAA	neutron activation analysis
NASH	non-alcoholic steatohepatitis
NDA	EFSA Panel on Nutrition, Dietetic Products and Allergies
NME	non-milk extrinsic
NTP	National toxicology program
OGTT	oral glucose tolerance test
OHAT	Office of health assessment and translation
PAL	physical activity level
PC	prospective cohort studies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMETHEUS	PROmoting METHods for Evidence Use in Scientific assessments
QUICKI	Quantitative insulin sensitivity check index
RCT	randomised controlled trial
RI	Reference Intake range
RoB	risk of bias
SBP	systolic blood pressure
SACN	UK Scientific Advisory Committee on Nutrition
SSB	sugar-sweetened beverage
SSD	sugar-sweetened soft drinks
T2DM	type 2 diabetes mellitus
TG	triglycerides
Total-c	total cholesterol
UL	Tolerable upper level of intake
VAT	visceral adipose tissue
VLDL-c	very low-density lipoprotein cholesterol
WG	Working Group
WHO	World Health Organization

Appendix A – Overview of dietary reference values and recommendations

In 2010, in the context of setting dietary reference values for carbohydrates and dietary fibre, the European Food safety Authority (EFSA NDA Panel, 2010a) concluded that the available data **did not allow the setting of a UL for total or added sugars**, neither an Adequate Intake (AI) nor a Reference Intake range (RI). However, evidence on the relationship between patterns of consumption of sugar-containing foods and **dental caries**, **weight gain** and **micronutrient intake** should be considered when establishing nutrient goals for populations and recommendations for individuals and when developing food-based dietary guidelines (FBDG).

The evidence-based Guideline of the German Nutrition Society (GNS) on carbohydrate intake and prevention of nutrition-related diseases (Hauner et al., 2012) recommended reducing the consumption of SSBs, but did **not provide a quantitative limit for sugar intake** or any components of this. The basis for this recommendation was probable evidence that high consumption of SSBs increases the risk of obesity and type 2 diabetes in adults, and the high consumption of SSBs particularly among adolescents and young adults in Germany.

The Nordic Nutrition Recommendations (Nordic Council of Ministers, 2014) limited the intake of **added sugars** (sucrose, fructose and starch hydrolysates) to **< 10% of the total energy intake** for the general population to ensure adequate intakes of micronutrients and dietary fibre (**micronutrient density of the diet**), which was found particularly important for children and persons with a low energy intake. It was also recommended to limit the consumption of SSBs because associated with an increased **risk of type 2 diabetes** and **excess weight gain**, and to avoid frequent consumption of sugar-containing foods to reduce the **risk of dental caries**.

The UK Scientific Advisory Committee on Nutrition (SACN, 2015) recommended that the average population intake of **free sugars** (all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus sugars naturally present in honey, syrups and unsweetened fruit juices) should not exceed **5% of total energy intake** for age groups from 2 years upwards. Evidence from intervention studies showing that increasing sugars intake **increases energy intake** in individuals consuming an *ad libitum* diet and that SSBs are linked to **weight gain** in children and adolescents, and evidence from prospective cohort studies showing that the consumption of sugars is associated with increased **risk of dental caries** and intake of SSBs are associated with an **increased risk of type 2 diabetes** mellitus were at the basis of this recommendation.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) issued an opinion on the establishment of recommendations on sugar intake (ANSES, 2016). The opinion focused on the metabolic effects of sugars in food, whether naturally present or added, and their involvement in the development of chronic diseases (metabolic diseases, cancer and cardiovascular diseases). ANSES set an upper intake limit for **total sugars** of **100 g/day** for the adult healthy population, which excludes lactose and galactose naturally present in milk and dairy products. The upper intake limit was calculated from the minimum daily consumption of fructose (50 g) for which a significant increase in **blood concentrations of triglycerides** was observed in intervention studies, and considering that an intake of 50 g of fructose corresponds to an intake of 100 g of sucrose.

The Institute of Medicine of the US National Academy of Sciences (IoM, 2005) concluded that there was **insufficient evidence to set a UL for added sugars** (sugars and syrups that are added to foods during processing or preparation). However, a maximal intake level of **≤ 25% of total energy intake** was suggested to prevent the displacement of foods that are major sources of essential micronutrients (**micronutrient density of the diet**).

The 2015–2020 Dietary Guidelines for Americans (HHS/USDA, 2015) recommended that individuals aged 2 years and older should derive **< 10% of total energy intake** from **added sugars** in order to achieve healthy eating patterns within calorie limits (**micronutrient density of the diet**). This recommendation was based on food pattern modelling and national data on intakes of calories from added sugars.

The World Health Organization (WHO) appraised the evidence available on the effects of **free sugars** on the risk of non-communicable diseases in adults and children, with a particular focus on **weight gain** and **dental caries** (WHO, 2015). The WHO recommended reducing the intake of free sugars to **< 10% of total energy intake** in both adults and children, with a **conditional** recommendation to reduce it further to **< 5% of total energy intake**.

Finally, two professional associations have issued recommendations on sugar intake for children only (up to 18 years of age).

The American Heart Association (AHA) reviewed the scientific evidence on the cardiovascular health effects of **added sugars** in **children** (Vos et al., 2016). Strong evidence was found to support an association between the intake of added sugars and **increased cardiovascular disease risk** in children through **increased energy intake**, **increased adiposity** and **dyslipidaemia**. AHA provided recommendations that **added sugars** (all sugars used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table) should be consumed up to a **maximum amount** of **25 g per day** by **children > 2 years** of age and **avoided** by **children < 2 years** of age.

In 2017, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition (Fidler et al., 2017), reviewed the scientific evidence on the relationship between sugars intake and: (a) the development of sweet taste or flavour preference, and (b) health outcomes. The Committee concluded that a preference for sweet taste is driven by interplay of many factors and that the association between high consumption of SSBs in early and late childhood could not be demonstrated to be causal. Building on the conclusions reached by WHO (2015), SACN (2015) and the AHA (Vos et al., 2016) regarding the effect of sugars intake and different health outcomes in paediatric populations, the Committee recommended that intakes of **free sugars** should be reduced and minimised with a desirable **upper limit of < 5% energy intake in children and adolescents** aged 2–18 years. This represents 15–28 g of free sugars for girls and 16–37 g for boys. Intakes should be **even lower in infants and toddlers < 2 years**.

A tabulated overview of these recommendations is given in Table A.1.

Table A.1: Summary of existing recommendations on sugar intake

Guideline	Target population	Sugar fraction	Recommendation	Basis (endpoint)	Other endpoints assessed	Review method
EFSA NDA Panel (2010a)	General population	Added sugars	Consider when setting FBDGs	Dental caries Body weight Micronutrient density	Glucose homoeostasis, risk of T2DM, blood lipids, blood pressure, CVD risk	Narrative
German Nutrition Society (2012)	General population	SSBs	Limit consumption	Obesity Risk of T2DM	BP/hypertension, metabolic syndrome, CHD risk, cancer	Systematic
Nordic Council of Ministers (2014)	General population	Added sugars	< 10E%	Micronutrient density	Dental caries (frequency of intake), weight gain and risk of T2DM (SSBs), glucose homoeostasis, blood lipids, blood pressure, CVD risk, uric acid	Systematic
Health Council of the Netherlands (2015)	General population	SSBs	Limit consumption	Obesity Risk of T2DM	–	Systematic
SACN (2015)	General population (>2 years)	Free sugars	≤ 5E%	Energy intake	Dental caries (frequency of intake), weight gain and risk of T2DM (SSBs), blood lipids, blood pressure, CHD, glucose homoeostasis	Systematic
ANSES (2016)	Adults	Total sugars	100 g/day	Fasting triglycerides	Weight gain, glucose homoeostasis, blood lipids, intrahepatic lipids and risk of NAFLD, uric acid, blood pressure	Systematic
IoM (2005)	General population	Added sugars	< 25E%	Micronutrient density	CHD risk, energy intake, body weight, blood lipids, cancer	Narrative
HHS/USDA (2015)	General population	Added sugars	< 10E%	Micronutrient density	–	Food pattern modelling and national data on added sugars intake
WHO (2015)	General population	Free sugars	< 10E% < 5E% conditional	Body weight Dental caries	–	Systematic

Guideline	Target population	Sugar fraction	Recommendation	Basis (endpoint)	Other endpoints assessed	Review method
American Heart Association (2016)	Children	Added sugars	25 g/day ≥ 2 years Avoided < 2 years	Energy intake Adiposity Dyslipidaemia CVD risk	Micronutrient density, blood pressure, risk of NAFLD, glucose homoeostasis, risk of T2DM	Narrative
ESPGHAN (2017)	Children	Free sugars	≤ 5E% ≥ 2 years (lower for < 2 years)	Dental caries Weight gain (SSBs) CVD and T2DM (fructose)	Preference for sweet taste	Narrative/systematic

FBDG: food-based dietary guidelines; T2DM: type 2 diabetes mellitus; CVD: cardiovascular disease; SSB: sugar-sweetened beverage; CHD: coronary heart disease; NAFLD: non-alcoholic fatty liver diseases.

Appendix B – Systematic reviews and meta-analysis on the relationship between added/free sugars and their sources and surrogate/disease endpoints

A scoping literature search was performed to identify systematic reviews and meta-analysis published in English since 2009 addressing the health effects of added sugars/non-milk extrinsic sugars/free sugars or any of its dietary sources.

The full list of references identified is reported in Table B.1 together with the specific exposure and outcome(s) of interest. All reviews for which the exposure of interest was added, free or total sugars from all dietary sources are presented in Table B.2. Based on the inclusion criteria identified for subquestions 5 and 6 (see Section 9.1), reviews having the same or wider inclusion criteria were used as a basis to update or build new literature searches (see Section 9.2).

Table B.1: Overview of systematic reviews and meta-analysis published since 2009 on the relationship between sugars and their sources and endpoints of interest

Reference	Endpoint (population subgroup)	Exposure
Anderson et al. (2009)	Caries (adults and children)	Sucrose including sucrose-based carbonated soft drinks, baked goods, sweets and table sugar, as added to other foods and drinks
Auerbach et al. (2017)	Obesity (children)	Fruit juice
Avery et al. (2015)	Obesity (children)	SSBs
Bucher Della Torre et al. (2016)	Obesity (children)	SSBs
Chiavaroli et al. (2015)	Blood lipids (adults and children)	Fructose
Chiu et al. (2014)	NAFLD (adults)	Fructose
Chung et al. (2014)	Liver health (adults)	Fructose
Crowe-White et al. (2016)	Obesity (children)	Fruit juice
Fattore et al. (2017)	Blood lipids, blood pressure (adults)	Free sugars (fructose, sucrose and glucose)
Gibson (2008)	Obesity (adults and children)	Sugar-sweetened soft drinks (SSD)
Gibson et al. (2013)	Blood lipids, blood pressure, glucose metabolism (adults)	Sucrose
Greenwood et al. (2014)	Risk of T2DM	SSD
Huang et al. (2014)	Risk of CVD	SSBs
Imamura et al. (2015)	Risk of T2DM	SSB, fruit juice
Jayalath et al. (2014)	Blood pressure	Fructose-containing sugar (high-fructose corn syrup, sucrose and fructose)
Jayalath et al. (2015)	Blood pressure	SSBs containing free or bound fructose
Kaiser et al. (2013)	Obesity (adults and children)	SSBs
Kelishadi et al. (2014)	Blood lipids, blood pressure, glucose metabolism	Fructose

Reference	Endpoint (population subgroup)	Exposure
Keller and Bucher Della Torre (2015)	Blood lipids, Blood pressure, glucose metabolism, risk of CVD	SSBs
Kim and Je (2016)	Blood pressure	SSBs and artificially sweetened beverages
Ma et al. (2016)	Obesity (adults and children)	Fructose, glucose, SSB, HFCS
Malik et al. (2010)	Risk of T2DM	SSBs
Malik et al. (2013)	Obesity (adults and children)	SSBs
Malik et al. (2014)	Blood pressure	SSBs
Mattes et al. (2011)	Obesity (adults and children)	SSBs
Moynihan and Kelly (2014)	Dental caries (adults and children)	Total sugars, free sugars, added sugars, sucrose, NME sugars
Perez-Morales et al. (2013)	Obesity (children)	SSBs
SACN (2015)	Blood lipids, blood pressure, dental caries, glucose metabolism, obesity, risk of CVD, risk of T2DM	Total carbohydrate, sugars reported as a nutrient (fructose, sucrose, lactose, glucose), table sugar and other extrinsic sugars (syrups), food format (solid vs. liquid, which includes SSBs)
Singh et al. (2011)	Risk of gout (adults)	SSBs, fructose
Sonestedt et al. (2012)	Blood lipids, blood pressure, glucose metabolism, risk of CVD, risk of T2DM	SSBs, sugars, sucrose and fructose
Te Morenga et al. (2013)	Obesity (adults and children)	Free sugars
Te Morenga et al. (2014)	Blood lipids, blood pressure	Sugar (sucrose) or free sugars
David Wang et al. (2014)	Blood lipids	Fructose
Wang et al. (2014)	Glucose metabolism (adults)	Fruit juice
Xi et al. (2014)	Risk of T2DM	Fruit juice
Xi et al. (2015)	Blood pressure, risk of CVD	SSBs
Zheng et al. (2015)	Obesity (adults and children)	SSBs

SSB: sugar-sweetened beverage; NAFLD: non-alcoholic fatty liver diseases; T2D: type 2 diabetes mellitus; CVD: cardiovascular disease; HFCS: high-fructose corn syrup.

Table B.2: Selected systematic reviews with research question partially or completely overlapping with the present work

Systematic review	Subquestion 4					Subquestion 5
	Fattore et al. (2017)[(a)]	**SACN (2015)**	**Sonestedt et al. (2012)**	**Te Morenga et al. (2013)**	**Te Morenga et al. (2014)**	**Moynihan and Kelly (2014)**
Endpoints	BP, blood lipids and body weight	All	Glucose metabolism, BP, blood lipids, risk of T2D, risk of CVD	Obesity	BP, blood lipids	Caries
Databases	PubMed/MEDLINE, EMBASE, Cochrane Library Hand search	Medline MEDLINE In-Process & Other Non-Indexed Citations Embase CAB Abstracts ISI Web of Science BIOSIS The Cochrane Library Hand search	PubMed SveMed+	OVID Medline, Embase PubMed, CiNAHL, Scopus, Web of Science	OVID Medline, Embase PubMed, CiNAHL, Scopus, Web of Science Grey literature Hand search	MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, LILACS, CNKI, Wanfang South African Department of Health databases
Search dates	Up to 22 October 2015	1990–December 2010	January 2000–October 2010Update November 2010–December 2011	Up to December 2011	1960–August 2013	1950–November 2011
Language limit	English	English	English or a Nordic language	English	English	No limit
Study type	Intervention studies	RCT PC	RCT PC	RCT PC	RCT	Intervention, cohort, population or cross-sectional
Study duration	≥ 2 weeks	RCT > 6 weeks (≥ 3 days for energy intake/satiety) PC > 3 years	RCT ≥ 4 weeks (drop out ≤ 50%) PC ≥ 4 years	RT ≥ 2 weeks PC ≥ 1 year	RCT≥ 2 weeks	
Population	Adults	Adults/children	Adults/children	Adults/children	Adults/children	Adults/children

BP: blood pressure; T2D: type 2 diabetes; CVD: cardiovascular disease; RCT: randomised controlled trial; PC: prospective cohort studies.
(a): Not used as primary source of information as the endpoints were assessed under isocaloric conditions.

Appendix C – Questionnaire to National Competent Authorities of European countries

NAME: ☐

COUNTRY: ☐

ALIGFFILIGLIATION: ☐

E MAIL: ☐

DATE: ☐

- EFSA has been requested to provide a scientific opinion on the Tolerable Upper Intake Level of dietary sugars. The assessment concerns the main types of sugars (mono- and disaccharides) found in mixed diets (i.e. glucose, fructose, galactose, sucrose, lactose, maltose and trehalose). Sugar alcohols (polyols), other substances used as sugar replacers, and other mono- or disaccharides present in the diet in marginal amounts, are not included in the term "sugars" for the purpose of this assessment. In this context, EFSA will address:
  - **Total sugars:** i.e. the monosaccharides glucose, fructose, and galactose, and the disaccharides sucrose, lactose, maltose and trehalose present in foods;
  - **Added sugars:** sugars used as ingredients in processed and prepared foods and sugars eaten separately or added to foods at the table; and
  - **Free sugars:** added sugars plus sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.

In the context, EFSA would like, through this questionnaire, to gather information on the following:

a) Data available from national food consumption surveys (or regional food consumption surveys e.g. targeting specific population groups such as infants or pregnant women) on the intake of **total/added/free sugars**;
b) National food composition data on **total, added and free sugars** if available, together with a description of the methods used to estimate **added** and **free sugars** in foods;
c) National dietary recommendations on the amount of sugars (whether total, added or free) to be consumed in the diet, if available.

To answer this questionnaire, please tick the relevant boxes. If you have doubts or queries in relation to the compilation of this questionnaire, please contact us at: nda@efsa.europa.eu

1) Please specify the last national food consumption survey(s) carried out in your country, indicating the year (or time frame) in which the survey was conducted, the method used for data collection (food diaries, food records, 24-h dietary recalls, other), the number of days in which data was collected for each subject, and the age group(s) included in the survey. Regional food consumption surveys should only be indicated if they targeted specially infants (up to 12 months of age) or pregnant women. Food consumption surveys using food–frequency questionnaires for data collection should not be included.

Name of survey	Type of survey (National/regional)	Year (range)	Method for data collection	Number of days/subject	Age groups included

Add as many rows as needed.

2) Please indicate whether there are publications available (in any language) on the intake of total sugars, added sugars, and/or free sugars in your country at national level (i.e. from the most recent national food consumption surveys that you have listed in question 1):

Author/year	Total sugars	Added sugars	Free sugars
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no
	☐ yes ☐ no	☐ yes ☐ no	☐ yes ☐ no

Add as many rows as needed.

Please provide the full list of references, as well as the full text if available to you ☐

Note: *Should you wish to share data not published yet but soon to be (i.e. on a confidential basis/embargo until publication), please specify the foreseen/assumed date of publication, and note that only data published by March 2019 will be accepted. Please also specify if you have anything against sharing unpublished data with the Experts of the Working Group on Sugar, for the purposes of this risk assessment.*

If NO publications are available on the intake of total sugars, added sugars, and/or free sugars in your country at national level → please go directly to question 5.

3) The national food composition database used to calculate the intake of total sugars, added sugars, and/or free sugars in the afore-mentioned publications contains data on:

Total sugars ☐ yes ☐ no

Glucose ☐ yes ☐ no

Fructose ☐ yes ☐ no

Sucrose ☐ yes ☐ no

Lactose ☐ yes ☐ no

Other sugars ☐ yes ☐ no. If yes, please specify ☐

Please provide the link to a website where the database can be downloaded from or a contact address/details of the person(s) responsible for the maintenance/update of the database ☐

4) Your national food composition database contains information on:

Added sugars ☐ yes ☐ no

Free sugars ☐ yes ☐ no

If the answer to any of the above is yes, please specify in detail the methodology that has been used to estimate the content of added sugars and/or free sugars in foods ☐

5) Does your country have some type of national recommendations on the amount of sugars to be consumed in the diet?

☐ yes ☐ no

If the answer is no → please go directly to question 9.

6) Please specify the national dietary recommendations to limit the amount of sugars consumed in the diet available in your country, indicating the type of recommendation (e.g. in the context of setting dietary reference values for nutrients, in the context of developing Food–Based Dietary Guidelines (FBDG)) and who was involved in their development (government bodies, scientific societies, industry, non-profit organisations, other), and the year in which the recommendation was issued. Please provide a link to the full text of the recommendation, if available. If more than one national recommendation is available in your country (e.g. established by different bodies; FBDGs targeting only specific age groups), use as many rows as needed.

a) National dietary recommendation: ☐ Body/organisation ☐ Year ☐

b) National dietary recommendation: ☐ Body/organisation ☐ Year ☐

c) National dietary recommendation: ☐ Body/organisation ☐ Year ☐

7) National recommendations on the consumption of dietary sugars (total, added and/or free) are directed to:

Please note that age ranges below are only indicative

☐ General population
☐ Infants (up to 12 mo)
☐ Old adults (>65 years)
☐ Young children (1-3 years)
☐ Adults (18-65 years)
☐ Pre-school children (3-6 Years)
☐ Adolescents (14-18 years)
☐ Schoolchildren (6-14 years)
☐ Others ☐
☐ Pregnant women
☐ Lactating women

8) Which diet-related health problems were considered when developing recommendations for the intake of total, added and/or free sugars consumption in your country? Please tick as many as needed:

☐ Cardiovascular diseases
☐ Cognitive impairement
☐ Dyslipidaemia
☐ Dental caries
☐ Hypertension
☐ Overweight/obesity
☐ Diabetes
☐ Cancer
☐ Nutrient deficiencies
☐ Adverse pregnancy outcomes
☐ Others (please specify) ☐
☐ None

9) Please add any general or specific comment, you might have: ☐

We kindly ask you to send back the filled survey by e-mail to: nda@efsa.europa.eu

Thank you very much for your participation in this survey

Appendix D – Exposure and endpoints search terms for subquestions 4 and 5

Subject index terms, where available, will be combined with free-text terms. Free-text terms will be searched in title and abstract fields in Embase and PubMed; and in title, abstract and keyword fields in the Cochrane Library databases and Scopus.

Exposure

Free sugars		
Subject index terms[6]		**Free-text terms[7] (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, PubMed)	**Emtree (Embase)**	
"Monosaccharides"[Mesh:noexp] "Glucose"[Mesh:noexp] "Fructose"[Mesh] "Galactose"[Mesh] "Disaccharides"[Mesh:noexp] "Sucrose"[Mesh:noexp] "Lactose"[Mesh] "Trehalose"[Mesh] "Maltose"[Mesh] "Dietary Sugars"[Mesh] "Dietary Sucrose"[Mesh] "High Fructose Corn Syrup"[Mesh] "Honey"[Mesh] "Molasses"[Mesh] "Carbonated Beverages"[Mesh] "Energy Drinks"[Mesh] "Fruit and Vegetable Juices"[Mesh] "Beverages/adverse effects"[Mesh] "Candy"[Mesh] "Chocolate"[Mesh]	'sugar intake'/exp 'glucose intake'/exp 'fructose intake'/exp 'lactose intake'/exp 'sugar'/exp 'monosaccharide'/de 'glucose'/exp 'fructose'/exp 'galactose'/exp 'disaccharide'/de 'sucrose'/exp 'maltose'/exp 'lactose'/exp 'trehalose'/exp 'syrup'/exp 'honey'/exp 'molasses'/exp 'sweetened beverage'/exp 'soft drink'/exp 'energy drink'/exp 'sports drink'/exp 'fruit and vegetable juice'/exp 'carbonated beverage'/exp 'confectionary'/de 'sugar confectionary'/exp	Sugar* OR Sucrose* OR Fructose* OR Galactose* OR Lactose* OR Trehalose* OR Maltose* OR Glucose* + dieta* OR diete* OR diet OR diets OR intake* OR consum* OR feed* OR food OR foods OR supplement* Disaccharide* Di saccharide* Monosaccharide* Mono saccharide* Simple carbohydrate* Refined carbohydrate* Syrup* Honey Candy Candies Sweet Sweets Sweetened Pastr* Confection* Patisserie Soft + drink* OR beverage* Softdrink* Fizzy + drink* OR beverage* Carbonated + drink* OR beverage* Soda + drink* OR beverage Energy + drink* OR beverage* Sports + drink* OR beverage* SSBs OR SSDs + beverage OR drink SSB OR SSD + beverage OR drink Juice* Smoothie*

[6] [Mesh] indicates that the MeSH term will be exploded, including in the search the terms below in the MesH hierarchy if available. [Mesh:noexp] indicates that the MesH term will not be exploded, the terms below in the MeSH hierarchy will not be searched. /exp indicates that the Emtree term will be exploded, including in the search terms below in the Emtree hierarchy if available. /de indicates that the Emtree term will not be exploded, the terms below in the Emtree hierarchy will not be searched.

[7] Asterisk symbol '*' indicates truncation. Plus sign '+' indicates the search terms will be linked with the Boolean operator AND.

Endpoints

Adipose tissue		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Adipose Tissue"[Mesh:noexp] "Abdominal Fat"[Mesh:noexp] "Intra-Abdominal Fat"[Mesh] "Subcutaneous Fat, Abdominal"[Mesh] "Subcutaneous Fat"[Mesh] "Body Weights and Measures"[Mesh:noexp] "Body Fat Distribution"[Mesh] "Adiposity"[Mesh] "Body Mass Index"[Mesh] "Body Size"[Mesh:noexp] "Body Weight"[Mesh: noexp] "Body Weight Changes"[Mesh] "Weight Gain"[Mesh] "Weight Loss"[Mesh]Overweight[Mesh] Obesity[Mesh:noexp] "Obesity, Morbid"[Mesh] "Pediatric Obesity"[Mesh] "Obesity, Abdominal"[Mesh] "Sagittal Abdominal Diameter"[Mesh] "Waist Circumference"[Mesh] "Body Composition"[Mesh] "Body Constitution"[Mesh:noexp]	'adipose tissue'/de 'abdominal fat'/exp 'abdominal subcutaneous fat'/exp 'intraabdominal fat'/exp 'body fat'/exp 'body fat distribution'/exp 'fat pad'/exp 'weight, mass and size'/de 'body weight'/de 'lean body weight'/exp 'body weight change'/exp 'body weight fluctuation'/exp 'body weight gain'/de 'body weight loss'/exp 'body weight variation'/exp'obesity'/exp 'body mass'/exp 'body size'/exp 'sagittal abdominal diameter'/exp 'waist circumference'/exp 'body composition'/de 'body distribution'/exp 'body constitution'/exp	Adipos* Fat pad Fat pads Body fat* Fatty tissue* Body size Abdominal fat Intra-abdominal fat Intraabdominal fat Fat distribut* Ectopic fat Waist circumference* Abdominal diameter Obese* Obesi* Obeso* Overweight* Weight + gain OR loss OR chang* OR reduc* OR maint* OR watch* OR variation OR control* OR Body OR lean Body mass Bmi Body composition* Body constitution*

Glucose homeostasis		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Diabetes Mellitus, Type 2"[Mesh]"Hyperinsulinism"[Mesh:noExp] "Insulin Resistance"[Mesh] "Metabolic Syndrome"[Mesh] "Blood Glucose"[Mesh] "Insulin/blood"[Mesh] "Hyperglycemia"[Mesh] "Glucose Intolerance"[Mesh] "Carbohydrate Metabolism"[Mesh] "Glycated Hemoglobin A"[Mesh] "Fructosamine"[Mesh] "Metabolic Diseases"[Mesh:NoExp]	'non insulin dependent diabetes mellitus'/exp'hyperinsulinism'/exp 'hyperinsulinemia'/exp 'insulin resistance'/exp 'metabolic syndrome X'/exp 'glucose blood level'/exp 'insulin'/exp AND 'blood'/exp 'hyperglycemia'/exp 'glucose intolerance'/exp 'hemoglobin A1c'/exp 'fructosamine'/exp 'fructosamine blood level'/exp 'metabolic disorder'/de	Diabet* + type 2 OR type II OR type2 OR typeii Late OR adult* OR matur* OR slow* OR stabl* + onset + diabetesNon-insulin-depend* + diabetes Noninsulin depend* + diabetes Hyperinsulinism Hyperinsulinemia Insulin + resistan* OR sensitivity OR tolerance OR intolerance OR control OR fasting Metabolic syndrome Glucose + tolerance OR intolerance OR fasting OR blood Hyperglycemia* Glycated OR Glycosylated + Hemoglobin OR haemoglobin Hemoglobin A Haemoglobin A Hemoglobin A1c Haemoglobin A1C Hemoglobin Aic Haemoglobin AiC HbA1c HbA(1c) HbA1 HbA 1c Hb A1c Hb a 1c Fructosamine + blood OR serum OR plasma

Cardiovascular system		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Cardiovascular Diseases"[Mesh] "Stroke"[Mesh] "Hypertension"[Mesh] "Prehypertension"[Mesh] "Atherosclerosis"[Mesh] "Ischemic Attack, Transient"[Mesh] "Heart Diseases"[Mesh] "Myocardial Ischemia"[Mesh] "Angina Pectoris"[Mesh] "Acute Coronary Syndrome"[Mesh] "Myocardial Infarction"[Mesh] "Non-ST Elevated Myocardial Infarction"[Mesh] "ST Elevation Myocardial Infarction"[Mesh] "Coronary Disease"[Mesh] "Cardiovascular System"[Mesh] "Blood Pressure"[Mesh] "Cholesterol"[Mesh:noExp] "Cholesterol, HDL"[Mesh] "Cholesterol, LDL"[Mesh] "Cholesterol, VLDL"[Mesh] "Dyslipidemias"[Mesh:noExp] "Hyperlipidemias"[Mesh:noExp] "Hypercholesterolemia"[Mesh] "Hyperlipoproteinemias"[Mesh] "Lipids "[Mesh] "Triglycerides"[Mesh] "Lipoproteins"[Mesh:NoExp] "Apolipoproteins"[Mesh]	'cardiovascular disease'/exp 'coronary artery disease'/exp 'cerebrovascular accident'/exp 'atherosclerosis'/exp 'transient ischemic attack'/exp 'heart infarction'/exp 'non ST segment elevation myocardial infarction'/exp 'ST segment elevation myocardial infarction'/exp 'acute coronary syndrome'/exp 'abnormal blood pressure'/de 'hypertension'/exp 'prehypertension'/exp 'heart disease'/exp 'angina pectoris'/exp 'heart death'/exp 'congestive heart failure'/exp 'cardiovascular system'/exp 'blood pressure'/exp 'cholesterol'/de 'cholesterol ester'/exp 'high density lipoprotein cholesterol'/exp 'low density lipoprotein cholesterol'/exp 'very low density lipoprotein cholesterol'/exp 'cholesterol metabolism'/exp 'disorders of cholesterol metabolism'/exp 'dyslipidemia'/exp 'hyperlipidemia'/exp 'hypercholesterolemia'/exp 'hypertriglyceridemia'/exp 'lipid blood level'/exp 'cholesterol blood level'/exp 'triacylglycerol blood level'/exp 'triacylglycerol'/exp	CV disease* CVD CVDs CHD CHDs Cardiovascular OR coronary OR heart OR cardiac + disease* OR disorder* OR event* OR risk* OR complication* OR outcome* OR morbidit* OR mortalit* OR death* OR failure* Stroke* Cerebrovascular accident* Apoplex* Acute coronary syndrome Angina* Stenocardia Heart muscle OR cardiac muscle OR myocardial OR myocardium OR cardiac OR coronary OR heart OR transient OR cardiomyophath* + ischemi* OR ischaem* Myocardial infarct* Heart attack* STEMI NSTEMI Blood pressure Arterial pressure Diastolic Systolic Blood pressure Prehypertens* Hypertens* Atherosclero* LDL-C HDL-C Cholesterol Hypercholesterol* Hypertriglycer*

	'lipoprotein'/de 'apolipoprotein B100'/exp 'apolipoprotein A1'/exp	Dyslipidemi* Dyslipoproteinemi* Hyperlipidemia* Hyperlipemi* Lipidemi* Lipemi* Hyperlipoprotein* Lipid Lipids Lipoprotein* Triglycerid* triacylglycerol Fasting TG Apolipoprotein* ApoB100 ApoB Apo B Apo B100 ApoA1 ApoA ApoAi Apo A Apo A1 Apo Ai

Liver function		
Subject index terms		**Free-text terms (Cochrane Library, Embase, PubMed, Scopus)**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	
"Fatty Liver"[Mesh:noexp] "Non-alcoholic Fatty Liver Disease"[Mesh] "Liver Cirrhosis"[Mesh:NoExp] "Liver Failure"[Mesh]	'liver fat'/exp 'fatty liver'/de 'nonalcoholic fatty liver'/exp 'liver cirrhosis'/exp 'liver fibrosis'/exp 'liver failure'/exp	Fatty liver NAFLD Steatohepatiti* Steatohepatiti* NASH Steatos* Fat liver accumul* Cirrhos* OR Fibros* OR failure* OR insufficienc* + liver OR Hepatic

Dental caries		
Subject index terms		**Free-text terms**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	**(Cochrane Library, Embase, PubMed, Scopus)**
"Oral health"[Mesh] "Dental Caries"[Mesh] "Cariogenic Agents"[Mesh] "DMF Index"[Mesh] "Diet, Cariogenic"[Mesh]	'dental health'/exp 'dental caries'/exp 'cariogenic agent'/exp 'cariogenic diet'/exp 'caries assessment'/exp 'DMF index'/exp 'DMFS index'/exp 'DMFT index'/exp	Oral health Dental health Caries Carious Cariogen* Dental OR teeth OR tooth OR root + decay* OR white spot* OR cavit* DMF DMFT DMFS DFT DEFT DEFS

Pregnancy outcomes		
Subject index terms		**Free-text terms**
MeSH (Cochrane Library, Pubmed)	**Emtree (Embase)**	**(Cochrane Library, Embase, PubMed, Scopus)**
"Birth Weight"[Mesh] "Fetal Macrosomia"[Mesh] "Fetal Weight"[Mesh] "Gestational Age"[Mesh] "Infant, Low Birth Weight"[Mesh] "Infant, Small for Gestational Age"[Mesh] "Infant, Very Low Birth Weight"[Mesh] "Infant, Extremely Low Birth Weight"[Mesh] "Diabetes, Gestational"[Mesh] "Pregnancy in Diabetics"[Mesh]	'birth weight'/exp 'high birth weight'/exp 'low birth weight'/exp 'small for date infant'/exp 'very low birth weight'/exp 'extremely low birth weight'/exp 'fetus weight'/exp 'gestational age'/exp 'tall stature'/de 'macrosomia'/exp 'large for gestational age'/exp 'pregnancy diabetes mellitus'/exp	Weight + birth OR newborn* OR new born* OR nenonat* OR fetal OR foetal OR fetus OR foetus Size + birth OR newborn* OR new born* OR neonat* OR fetal OR foetal OR fetus OR foetus Macrosomia* Macrosomatia* SGA OR LGA + infant* OR neonat* OR newborn* OR child* OR baby OR babies Gestational age OR gestation age OR gestational time OR gestation time "small for date" OR "large for date" + infant* OR neonat* OR newborn* OR child OR children OR baby OR babies Gestational OR pregnant* OR pregnanc* + diabetes DGM